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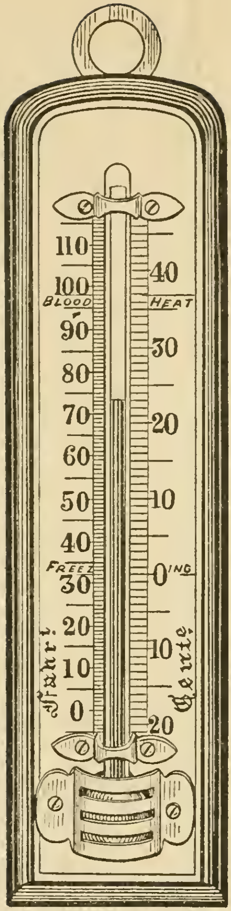

Thermometer Showing Comparison of Fahrenheit and Centigrade Scales

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Convenient Comparisons of Metric and Avoirdupois Weights

1 kilogram = 2.2046 pounds
1 pound = 453.6 grams
1 ounce = 28.3 grams

THE
ELEMENTS OF THE SCIENCE
OF
NUTRITION

BY

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To

CARL VON VOIT

MASTER AND FRIEND

FROM WHOM THE AUTHOR RECEIVED THE INSPIRATION

OF HIS LIFE'S WORK

THIS VOLUME IS DEDICATED.

PREFACE.

The aim of the present book is to review the scientific substratum upon which rests the knowledge of nutrition both in health and in disease. Throughout, no statement has been made without endeavoring to give the proof that it is true.

The widespread interest in the subject of nutrition at the present time leads the author to hope that this book may prove of value to the student of dietetics and to the clinical physician.

Laboratory methods to explain the inner processes in disease have been applied to hospital patients for twenty years or more in Germany, but in the United States little has been done in this regard. If such investigations are in any way promoted by their discussion here this writing will not have been in vain.

On a previous occasion the author collected the more important information concerning the life history of the mineral constituents of the body for the American Text Book of Physiology, and the subject has been allotted limited space in this volume.

The author would apologize to all whose claims of priority of discovery have not been duly recognized.

He wishes to express his great obligation to a former pupil, Dr. Margaret B. Wilson, who has painstakingly corrected the manuscript.

GRAHAM LUSK.

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NEW YORK, *October* 1, 1906.

CONTENTS.

THE ELEMENTS OF THE SCIENCE OF NUTRITION.

CHAPTER I.

INTRODUCTORY.

The earliest scientific observations concerning nutrition were founded upon the commonly noted fact that in spite of large quantities of food eaten, a normal man did not vary greatly in size from year to year. It was understood early in the history of physiology that the weight added by the ingestion of food and drink was lost in the urine, the feces, and the "insensible perspiration." The "insensible perspiration" was partly in evidence when moisture of the warm breath condensed upon a cold plate. By it was meant the usually invisible exhalations from the body, which are now known to be carbon dioxid and water.

Sanctorius[1] made many experiments upon himself and others to determine the amount of insensible perspiration. An old cut shows him sitting in a chair suspended from a large steelyard. As a matter of routine he determined his own weight previous to each meal and then weighted the steelyard so as to counterbalance the additional food he proposed to eat. During the meal when the chair dipped he ended his repast.

In Section I, Aphorism II, Sanctorius gives the following curious advice: "If a physician who has the care of another's health, is acquainted only with the sensible supplies and evacuations, and knows nothing of the waste that is daily made by the

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[1] Sanctorius: "De medicina statica aphorisimi," Venice, 1614. Translation by John Quincy, M.D., London, 1737.

insensible perspiration, he will only deceive his patient and never cure him." Aphorism III reads: "He only who knows how much and when the body does more or less insensibly perspire, will be able to discern when or what is to be added or taken away either for the recovery or preservation of health."

The modern era of the science of nutrition was opened by Lavoisier. The work of to-day is but the continuation of that done a century and more ago. Lavoisier and La Place made experiments on animal heat and respiration. The great German chemist Liebig derived his early training in Paris, residing there in 1822. Liebig's conception of the processes of nutrition fired the genius of Voit to the painstaking researches which laid the foundation of his Munich school. These have been repeated and extended by his pupils, of whom Rubner is chief, and by others the world over. Thus the knowledge often transmitted personally from the master to the pupil, to be in turn elaborated, had its seed in the intellect of Lavoisier. It was he who first discovered the true importance of oxygen gas, to which he gave its present name. He declared that life processes were those of oxidation, with the resulting elimination of heat. He believed that oxygen was the cause of the decomposition of a fluid brought to the lungs, and that hydrogen and carbon were produced in this fluid and then united with oxygen to form water and carbon dioxid. It was he who first made respiration experiments on man, the results of which are briefly described in a letter to Monsieur Terray,[1] written in Paris and dated November 19, 1790. There is no existing record of the apparatus with which Lavoisier worked and early obtained accurate results. The more important conclusions Lavoisier sums up as follows:

1. The quantity of oxygen absorbed by a resting man at a temperature of 26° C. is 1200 *pouces de France*[2] hourly.
2. The quantity of oxygen required at a temperature of 12° C. rises to 1400 *pouces*.

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[1] Report of the British Association for the Advancement of Science, Edinburgh, 1871, p. 189.

[2] 1 cubic pouce—0.0198 liters.

3. During the digestion of food the quantity of oxygen amounts to from 1800 to 1900 *pouces.*
4. During exercise 4000 *pouces* and over may be the quantity of oxygen absorbed.

These remarkable results are in strict accord with the knowledge of our own day. We know more details, but the fundamental fact that the quantity of oxygen absorbed and of carbon dioxid excreted depends primarily on (1) food, (2) work, and (3) temperature, was established by Lavoisier within a few years after his discovery that oxygen supported combustion.

It was, however, quickly noted that if carbon and hydrogen burned in the lungs, the greatest heat would be developed there, a result not in accordance with observation. It was then suggested that the blood dissolved oxygen, and that the production of carbon dioxid and water took place through oxidation within the blood. In 1837 Magnus discovered that the blood did hold large quantities of oxygen and carbon dioxid, which gave apparent support to this theory. Ludwig in his later years believed that the oxidation took place in the blood.[1] Through the critical studies of Liebig, which were published in 1842, it was seen that it was not carbon and hydrogen which burned in the body, but proteid, carbohydrates, and fat. Liebig's original theory was that while oxygen caused the combustion of fat and carbohydrates, the breaking down of proteid was caused by muscle work. It will be shown later that oxygen is not the cause of the decomposition of materials in the body, but that this decomposition proceeds from unknown causes, and the products involved unite with oxygen. These chemical changes of materials under the influence of living cells is known as *metabolism.* This process may involve two factors, *catabolism*, or the reduction of higher chemical compounds into lower, and *anabolism*, or the construction of higher substances from lower ones.

Liebig was also the father of the modern methods of organic analysis, and with him began the great accumulation of knowledge concerning the chemistry of the carbon compounds, in-

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[1] Verbal statement to the writer.

cluding the many products of the animal economy. These discoveries gave the world a knowledge of the constitution of foods, of urine, of feces, and of tissues, which was not possessed by Lavoisier.

Liebig applied to the problems of biology the mental wealth of the newer chemistry which he himself was creating. He knew that proteid contained nitrogen, and in 1842 he suggested that the nitrogen in the urine might be made a measure of the proteid destruction in the body.[1] The proof that such was the case was afforded by Carl v. Voit,[2] who established the fact that an animal could be brought into what he called nitrogenous equilibrium. In this condition the nitrogen of the proteid eaten was equal to the nitrogen eliminated from the body in the urine and feces. Thus Voit[3] fed a dog for fifty-eight days with 29 kilograms of meat containing 986.0 grams of nitrogen, and found 982.8 grams of nitrogen in the excreta of the period. The amount of N in the urine was 943.7 grams, and in the feces 39.1 grams. The difference between the amount of nitrogen ingested and that recovered in the excreta was only three-tenths of one per cent. It therefore seemed extremely probable that the excretory outlet for proteid nitrogen was in the urine and in the feces and that other sources of its loss were normally negligible. But in order to establish the fact it was necessary to consider the following questions:

Is the nitrogen of the air built up into organic compounds within the body? Is any proteid nitrogen given off as nitrogen gas? As ammonia gas? In the sweat? How much is lost through the growth of the hair, nails, and epidermis?

Lavoisier had said that nitrogen gas had nothing to do with respiration. Regnault and Reiset[4] sometimes found that animals under a bell-jar absorbed nitrogen gas and at other times

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[1] Liebig: "Die organische Chemie in ihrer Anwendung auf Physiologie und Pathologie," 1842.

[2] Voit: "Physiol. Chem. Untersuchungen," 1857.

[3] Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 35.

[4] Regnault and Reiset: "An. de chemie et phys.," Paris, 1849, Sec. 3, Tome xxvi.

gave it off. The quantity in both cases was extremely small. Voit explained this by showing that the blood and the tissues always contained nitrogen gas dissolved in proportion to the partial pressure of the gas in the atmosphere. A change of this partial pressure under the bell-jar would change the body's content of dissolved nitrogen and explain Regnault and Reiset's variations.

The experiments of Bachl[1] showed that a rabbit with a tracheal cannula could be made to expire for six hours through Nessler's reagent without the indication of a trace of ammonia in the breath. This has also been shown after making an Eck fistula in a dog,[2] where there is an increase in the amount of ammonia in the blood and in the urine. The lungs are not permeable to ammonia.[3] The ordinary insensible perspiration is not accompanied by any appreciable loss of nitrogenous excreta, although profuse sweating certainly brings out some urea, uric acid, and other nitrogen extractives normally excreted in the urine. The recent experiments of Benedict[4] show that the cutaneous excretions of a resting man may amount to 0.071 gram nitrogen per day; of a man at moderate work to 0.13 gram per hour, and at hard work to 0.22 gram per hour.

Voit[5] collected the hair and epidermis from a dog for 565 days and found an average daily output of 1.2 grams with 0.18 gram of nitrogen. Moleschott[6] cut the hair and nails of several men once a month. The daily outgrowth of hair was 0.20 gram with 0.029 gram of nitrogen, and of nail substance 0.005 gram with 0.0007 gram of nitrogen. The waste through the human epidermis has not been measured, but it must be very slight.

The above sources of error were thus shown to be negligible.

The view that the nitrogen of the urine and feces could be

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[1] Bachl: "Zeitschrift für Biologie," 1869, Bd. v, p. 51.

[2] Salaskin: "Zeitschrift für physiologische Chemie," 1898, Bd. xxv, p. 463.

[3] Magnus: "Archiv für ex. Pathologie und Pharmakologie," 1902, Bd. xlviii, p. 100.

[4] Benedict: "Journal of Biological Chemistry," 1906, vol. i, p. 263.

[5] Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 207.

[6] Moleschott: "Untersuchungen zur Naturlehre," Bd. xii, p. 187.

made a measure for the determination of proteid metabolism was thus securely established. Urea, the principal nitrogenous end-product derived from proteid, was therefore shown to be not an adventitious product, but one normally proportional to the proteid destruction. It was known that meat proteid in general contained about 16 per cent. of nitrogen, or 1 gram of nitrogen in 6.25 grams of proteid. Therefore for every gram of nitrogen found in the excreta, 6.25 grams of proteid have been destroyed in the body. It is evident that if proteid nitrogen be retained in the body a new construction of body tissue is indicated, whereas if more nitrogen is eliminated than is ingested with the food, a waste of body tissue must take place. The discovery of the method of calculating the proteid metabolism led Voit to suggest to Pettenkofer that he construct an apparatus with which the total carbon excretion might be measured, including that of the respiration as well as that of the urine and the feces. Voit saw that with these data it would be possible to determine just how much of each foodstuff was actually burned in the human body. He has described the delight which he and Pettenkofer experienced when their wonderful machine began to tell its tale of the life processes. The cost of the apparatus, which was considerable, was defrayed by King Maximilian II of Bavaria.

It has been stated that the form of Lavoisier's respiration apparatus is unknown. In 1850 Regnault and Reiset[1] published an account of respiration experiments in which small animals were placed under a bell-jar containing a known quantity of oxygen. The air was kept free from carbon dioxid by pumping it through potassium hydrate. The gaseous exchange between the animal and its environment could be readily ascertained, by determining the amount of carbon dioxid given off and the amount of oxygen absorbed. No attempt was made to determine from what materials the carbonic acid arose. The method of Regnault and Reiset placed the animals in a confined

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[1] Regnault and Reiset: "An. d. Chem. und Pharm.," 1850, Bd. lxxiii, pp. 92, 129, 257.

space where poisonous exhalations other than carbon dioxid could collect, and where the atmosphere became saturated with water. Although Regnault and Reiset had no idea of the materials which were oxidized in the animals with which they were experimenting, we find that Bischoff and Voit[1] tried to read such interpretations into the work of Regnault and Reiset. Thus Bischoff and Voit determined the quantity of nitrogen in the urine of a starving dog, which indicated that he had burned in twenty-four hours 218 grams of his own "flesh." The flesh was calculated from the nitrogen elimination on the basis of the knowledge that fresh meat contains 3.4 per cent of nitrogen. Many of the older experiments were computed on this basis. It was shown that the 218 grams of "flesh" contained 40 grams of carbon. Bischoff and Voit draw attention to an experiment of Regnault and Reiset, showing that a meat-fed dog of a weight similar to the above gives off 250 grams of carbon and absorbs 900 grams of oxygen in the respiration of twenty-four hours. These figures indicated to Bischoff and Voit that the extra carbon elimination was due to the combustion of fat, and they reached the conclusion that the waste of the body in starvation is dependent on the metabolism of proteid and fat. Correct results, however, were attainable only by combining the two methods, so that both the quantity of the nitrogen and carbon of the urine and feces, and the amount of carbon dioxid of the respiration during the same period of time could be ascertained. This was accomplished by the respiration apparatus of Pettenkofer.

The problem to be solved by Pettenkofer included the maintenance of a man in normal surroundings. A small room was therefore constructed which was well ventilated by a current of air. This air entered the chamber freely through an opening in connection with a large room outside and was aspirated from a second opening in the chamber, through a large gas-meter, where its volume was measured (500,000 liters per day). It

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[1] Bischoff and Voit: "Die Gesetze der Ernährung des Fleischfressers," 1860, p. 43.

was evidently impracticable to determine all the carbon dioxid in this large volume of air, but its amount was calculated from the analysis of duplicate samples continually withdrawn from the air leaving the chamber during the time of the experiment. Each sample, as it was pumped out, was made to pass over ignited pumice stone, soaked in sulphuric acid, to remove the water. Next it bubbled through baryta water to remove the carbon dioxid, and then passed through a small gas-meter, where the volume of the sample was measured. After this fashion the amount of carbon dioxid and water coming from the air of the chamber was determined in duplicate. Other duplicate analyses of the air taken outside the ventilator, just before it entered the chamber, were simultaneously made in the same manner as were the analyses of the chamber air itself. Knowing the quantity of carbon dioxid and water entering and leaving the room, it was easy to calculate how much was derived from the man living in it during the period of experimentation. The experimenters failed to find any other gaseous exhalation from a man, such as ammonia, hydrogen, or methane, which could vitiate their results. Control experiments were made by burning a candle or evaporating a known weight of water within the room. Analysis showed that the carbon dioxid and water so produced were measurable within one per cent. of error.

As an illustration of the practical working of the respiration apparatus the first experiment of Pettenkofer and Voit,[1] which gives the metabolism in a starving man, will be described. The man was allowed a small quantity of Liebig's extract of beef, as the experimenters did not at that time realize the very slight discomfort usually entailed by total abstinence from food. As Liebig's extract has no nutritive value, its effect has been counted out in the following description.

The subject, on entering the living-room of the apparatus, weighed 71.090 kilograms, and he drank during the day 1.0548 liters of water, making a total body weight of 72.1448 kilograms. Twenty-four hours later he weighed 70.160 kilograms and his

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[1] Pettenkofer and Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 478.

excreta had amounted to 0.7383 kilogram carbon dioxid, 0.8289 kilogram water in the respiration, and 1.1975 kilograms of urine. The final body weight plus all the excreta amounted to 72.9247 kilograms. A total body weight of 72.1448 kilograms was converted into a body weight plus excreta amounting to 72.9247. The difference is due to oxygen absorbed. The difference of 0.7799 kilogram represents the amount of oxygen needed to convert the body substance lost into the excretory products obtained. The tabular statement reads:

MAN—STARVATION.

	Kg.		Kg.
Weight at start	71.090	Weight at end	70.160
Water drunk	1.0548	Carbon dioxid	0.7383
		Water in respiration	0.8289
Oxygen absorbed	0.7799	Urine	1.1975
	72.9247		72.9247

The analysis of the urine showed 12.51 grams of nitrogen and 8.25 grams of carbon. A calculation gives the amount of carbon in the respiration as 201.3 grams. If we neglect the feces as being too small in starvation to influence the results, we find that the total carbon elimination for twenty-four hours was 209.55 grams, and the total nitrogen 12.51. In the Liebig extract ingested there were 2.44 grams of carbon and 1.18 grams of nitrogen, which must be deducted from the above in order to obtain the strict loss of carbon and nitrogen from the body during the period of starvation. These values are:

C	207.11	grams.
N	11.33	"

These two figures enabled Pettenkofer and Voit to calculate what substances had burned in the body. As every gram of nitrogen in the excreta is approximately represented by the destruction of 6.25 grams of meat proteid, the amount of such proteid destroyed by the man was 70.81 grams. It has been found that for every gram of nitrogen present in meat proteid there are 3.28 grams of carbon. It is therefore easy to estimate that destruction of proteid represented by 11.33 grams of nitrogen involved the elimination of 37.16 grams of carbon. Now, the man eliminated 207.11 grams of total carbon, from which this proteid carbon may be deducted, leaving as residue 169.95 grams, which must have originated from a source other than proteid. The possible sources are two in number—carbohydrates and fats. In starvation no carbohydrates are ingested and their supply in the form of reserve glycogen is usually counted as being negligible in such experiments as these. The only other source from which the 169.95 grams of extra carbon could have been derived is fat, and as fat contains 76.52 per cent. of carbon, a destruction of 222.1 grams of fat may be calculated. This fasting man therefore destroyed:

Proteid	70.81	grams.
Fat	222.1	"

That such metabolism actually did take place was further indicated by the comparison of the amount of oxygen needed for the destruction of the above constituents, and the amount of oxygen absorption as determined by the experiment.

From the constituents of the proteid and fat destroyed, Pettenkofer and Voit deducted the constituents of the urine, which contains part of the C and H belonging to proteid. The balance of the carbon and hydrogen was fit for oxidation to carbon dioxid and water. Their calculation may thus be presented:

	Weight in Grams.		
	C.	H.	O.
Composition of the proteid burned	37.16	5.8	17.1
Composition of fat burned	169.95	25.7	25.1
Total C, H and O metabolized	207.11	31.5	42.2
Deduct quantity in the urine	8.2	2.0	7.6
Balance available for respiratory CO_2 and H_2O	198.9	29.5	34.6
Oxygen required	530.4	235.7	

Total O required for the formation of CO_2 and H_2O	766.1
Less O in the proteid and fat	34.6
Oxygen actually required	731.5
Oxygen absorption as determined	779.9
Difference	48.4

We may reach the same result by using the most modern figures for the oxygen requirement in the metabolism of the foodstuffs. We now know that to burn 100 grams of meat proteid requires 133.43 grams of oxygen, and to burn 100 grams of fat requires 288.5 grams, and to burn 100 grams of starch 118.5 grams. This being true, there are required:

	OXYGEN.
For 70.81 grams proteid	94.44 g.
For 222.1 " fat	639.55 g.
Total required	733.99 g.
Oxygen absorption as found	779.9 g.
Difference	45.91

Had carbohydrates burned, less oxygen would have been needed, since carbohydrates contain a larger proportion of oxygen than fats. Had the extra 169.95 grams of carbon been due to the combustion of starch (or glycogen), 382 grams would have burned, requiring 452.7 grams of oxygen instead of 639.5 grams for fat. Pettenkofer and Voit found in the amount of oxygen absorption a confirmation of their belief that the fasting organism supports itself by the combustion of its own proteid and fat.

It is apparent from this discussion that the quantity of oxygen needed in metabolism depends upon the kind of material that burns in the organism, and also that the relation between the amount of oxygen absorbed and carbon dioxid excreted depends on the same factor. Regnault and Reiset frequently observed that this latter relationship was variable. The relation of the *volume* of oxygen inspired to the *volume* of carbon dioxid expired is called the *respiratory quotient.* When carbohydrates burn, the R. Q. is unity; that is, for every hundred volumes of carbon dioxid excreted a hundred volumes of oxygen are absorbed. When proteid burns the quotient $\frac{\text{Vol. CO}_2}{\text{Vol. O}_2} = \frac{78.1}{100}$ or 0.781, and when fat burns the quotient is 0.71. Pettenkofer and Voit calculated that the respiratory quotient in their fasting man was 0.69. This indicated a combustion of fat in the organism.

The further researches of Pettenkofer and Voit were founded on the principles described in the above experiment on a fasting man. If meat and fat were ingested, the carbon and nitrogen excreta were collected, and from these data it was determined how much of each foodstuff was burned and whether there was a storage of either in the body or a loss of either from the body. If a mixed diet which included carbohydrates were given, the carbon dioxid elimination increased and the oxygen absorption was such as indicated the combustion of carbohydrates. It was assumed that after deducting the proteid carbon from the total carbon eliminated, the balance of extra carbon was derived from the destruction of the carbohydrates in so far as these were ingested; any carbon in excess of this was attributed to fat combustion.

Voit[1] in his necrology of Pettenkofer writes: "Imagine our sensations as the picture of the remarkable processes of the metabolism unrolled before our eyes, and a mass of new facts became known to us! We found that in starvation proteid and fat alone were burned, that during work more fat was burned, and that less fat was consumed during rest, especially during sleep; that the carnivorous dog could maintain himself exclusively on a proteid diet, and if to such a proteid diet fat were added, the fat was almost entirely deposited in the body; that carbohydrates, on the contrary, were burned no matter how much was given, and that they, like the fat of the food, protected the body from fat loss, although more carbohydrates than fat had to be given to effect this purpose; that the metabolism in the body is not proportional to the combustibility of the substances outside the body, but that proteid which burns with difficulty outside metabolizes with the greatest ease, then carbohydrates, while fat, which readily burns outside, is the most difficultly combustible in the organism."

Since the days of these researches repeated experiments have established the verity of the conclusions drawn. It is interesting to note that among the earliest experiments made

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[1] Voit: "Zeitschrift für Biologie," 1901, Bd. xli, p. 1.

were some upon patients in pathological conditions, one suffering from leukemia, the other from diabetes.

Besides the influence of foods upon metabolism, the changes brought about by exercise, temperature, and drugs were investigated, not only by the Munich school, but by many other workers. Similar investigations are actively progressing to-day.

Among the important conclusions reached by Voit was that concerning the manner of the metabolism. It has been stated that Liebig believed that fat and carbohydrates were destroyed by oxygen, while proteid metabolism took place on account of muscle work.

Voit[1] showed that muscle work did not increase proteid metabolism and that the metabolism was not proportional to the oxygen supply. The oxygen absorption apparently depended upon what metabolized in the cells. He showed that although fat burned readily in the air, it burned only with great difficulty in the body; and that proteid burned with comparative difficulty in the air, but went to pieces very readily in the body. Voit believed that the cause of metabolism was unknown, that the process was one of cleavage of the food molecules into simpler products, which could then unite with oxygen. Yeast cells, for example, convert sugar into carbonic acid and alcohol without the intervention of oxygen. In like manner the first products of the decomposition of fat, sugar and proteid, are formed in metabolism through unknown causes. Some of these preliminary decomposition substances may unite with oxygen to form carbon dioxid and water, others may be converted into urea, while others under given circumstances may be synthesized to higher compounds. In any case the absorption of oxygen does not cause metabolism, but rather the amount of the metabolism determines the amount of oxygen to be absorbed.

The statement is frequently met with in the literature of the subject that such and such a disease is the consequence of deficient oxidative power in the tissues. For example, it has recently been

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[1] Voit: "Zeitschrift für Biologie," 1869, Bd. v, p. 169; Bd. ii, p. 535.

stated that alcohol decreases the oxidative power of the liver for uric acid.[1] Such apparent decrease in oxidative power may however be due to the fact that the normal oxidizable cleavage products are not formed and therefore no oxidation can take place. It is not due to lack of oxygen that sugar does not burn in diabetes, or cystin in cystinuria. There is the normal supply of oxygen present, but the cleavage of these substances into bodies which can unite with oxygen cannot be effected, and hence they cannot burn.

Voit's pupil, Lossen,[2] showed that the carbon dioxid elimination in respiration was independent of the ventilation of the lungs except in so far as forced breathing increased the muscular work and the consequent output of carbon dioxid.

Pflüger,[3] who through different reasoning came to the same conclusion as Voit, devised an experiment in which a rabbit breathed quietly through a cannula, and the oxygen absorption was compared with that of the same animal when rapid artificial ventilation of the lungs with air took place, producing apnea or hyperarterialization of the blood. There was no difference, as is seen from the following table:

	Oxygen Absorbed in C.C. During 15 Minutes.	
	Normal respiration.	Apnea.
Series I	201.66	203.88
Series II	203.21	210.47

From these experiments it is made sure that the respiration does not cause or regulate metabolism. On the contrary, the metabolism regulates the respiration. The metabolism of the tissues, through its oxygen requirement and its carbon dioxid production, changes the condition of the blood and thereby

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[1] Beebe, S. P.: "American Journal of Physiology," 1904, vol. xii, p. 36.

[2] Lossen: "Zeitschrift für Biologie," 1866, Bd. ii, p. 244; and 1870, Bd. vi, p. 298.

[3] Pflüger: "Archiv für die ges. Physiologie," 1877, Bd. xiv, p. 1.

regulates the respiration. These distinctions are of fundamental importance.

Thus far the history of the principles which underlie the exact measurement of the metabolism has been briefly given. By metabolism is meant the chemical changes of materials under the influence of living cells. The first cause of these chemical changes, it has been seen, is unknown, but their results lead to motions of the smallest particles of protoplasm, motions whose totality we call life. Phenomena of life are phenomena of motion, due to liberation of energy in the breaking down of molecules. The motions are principally manifested as heat, mechanical energy and electric currents. In the organism mechanical energy may be converted into heat, as appears when the work of the heart is converted into heat by the friction of the blood upon the capillaries. Also the current of electricity developed at each systole of the heart, or in any other active tissue, is resolved into heat. Thus heat may become a measure of the total activity of the body. It is derived from the total metabolism and must be dependent on it and be a measure of it. Hence the physical activities noted in life are the results of chemical decompositions. Metabolism vivifies the energy potential in chemical compounds.

Lavoisier[1] was the first to recognize that animal heat was derived from the oxidation of the body's substance and to compare animal heat to that produced by a candle. To prove this he burned a known quantity of carbon in an ice-chamber and noted the amount of ice melted. He then calculated the amount of heat produced from a unit of carbon. He and La Place put a guinea-pig in an ice-chamber and noted the amount of ice which melted during ten hours and calculated the heat given off from the animal. They then determined how much carbon dioxid the guinea-pig gave off. The animal yielded 31.82 calories to the ice-chamber, while a calculation from the respiratory analysis showed that 25.408 calories could have been

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[1] For this literature see Rubner: "Zeitschrift für Biologie," 1893, Bd. xxx, p. 73.

derived by the burning of enough carbon to yield the same amount of carbon dioxid as was eliminated by the animal.

Lavoisier realized several of the errors in his work. For example, the calorimetric determination on the animal was made at a different temperature from that of the respiratory experiment, and Lavoisier knew that cold would raise the carbon dioxid output. Also cold reduced the heat in the animal itself, and, further, the water of respiration was added to that of the melting ice. But Lavoisier concluded that the source of the heat lay in the oxidation of the body.

Crawford, in England, found after burning wax and carbon, or on leaving a live guinea-pig in his water calorimeter, that for every hundred ounces of oxygen used the water was raised the following number of degrees Fahrenheit:

Wax	2.1
Carbon	1.93
Guinea-pig	1.73

Crawford concluded that the heat above produced was due to the transformation of pure air into fixed air (carbon dioxid) and water.

The method of Crawford was in reality one of considerable accuracy. According to the modern computation of Zuntz and Hageman[1] the following are the values of heat production where one liter of oxygen is used to burn the different foodstuffs in the body:

	Calories.
1 liter of oxygen used in the metabolism of proteid yields	4.691
1 " " " " " " " fat "	4.686
1 " " " " " " " starch "	5.046

This table shows that there is a maximum variation of only 7 per cent. in the heat value of a unit of oxygen to the body. Hence the quantity of oxygen absorbed may be utilized as an approximate indicator of heat production (Fig. 9, p. 259).

In 1823 the French Academy offered a prize for the best essay on the subject of animal heat. Depretz and Dulong competed for the prize and it was awarded to the former.

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[1] Zuntz and Hageman: "Stoffwechsel des Pferdes," 1898, p. 245.

Depretz[1] calculated the amount of heat which would have been liberated in burning the carbon and hydrogen of the metabolism to carbon dioxid and water, and compared this with the amount of heat given off by the animal. The heat as calculated was only 74 to 90 per cent. of what was found. So Depretz concluded that although the respiration was the principal source of animal heat, food, the motion of the blood, and friction yielded the remainder. Interpretation along the lines of the law of the conservation of energy was obviously beyond the ideas of the time.

Dulong's[2] experiments also led to the same conclusion, that oxidation was insufficient to explain the cause of animal heat, and that there must be other sources of it.

In 1851 R. Mayer laid down the law of the conservation of energy, and Helmholtz demonstrated its general applicability.

Energy cannot arise from nothing, nor can energy disappear into nothing. Where energy is active it must have been elsewhere potential. The sum total of energy remains constant in the universe, but energy may vary in kind. The kinds include mechanical energy, heat, electricity, magnetism, and potential energy. The source of energy on the earth is the sun, excepting the energy of the tides, which is due principally to the moon. The sun unevenly warms the atmosphere, producing winds which drive ships, and windmills. The sun's heat lifts the vapor of water into the atmosphere, producing rain, in consequence of which rivers are made to turn machinery. The sunlight acts upon a mixture of hydrogen and chlorin gas, causing them to unite with a loud explosion, and the sun acts upon the green leaf of the plant, causing it to unite carbon dioxid and water, with the production of formic aldehyde, which is built up into sugar, oxygen being given off in the process. The sun's energy required to build up the compound becomes latent or potential in it. Whenever and wherever this sugar is again converted into carbon dioxid and water by oxidation, exactly the

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[1] Depretz: "Annal. de chim. et de phys.," 1824.

[2] Dulong: *Ibid.*, 1841.

same quantity of energy taken from the sun and made potential in the sugar is set free. This sugar in the plant may be further converted into starch, cellulose, fat, and possibly into proteid. Plants furnish wood and coal as fuel for the steam-engine. They also furnish the basis of animal food, yielding substances which can build up animal tissues, and which can furnish the energy necessary to maintain those motions in the cells whose aggregate is called life. These motions appear in the body as heat, mechanical work, and electric currents, all of which may be measured as heat. Is this heat production completely derived from the metabolism? This question is but the continuation of the old one of Lavoisier in the light of newer science.

Bischoff and Voit[1] in 1860 still calculated the heat value of the metabolism from the heat developed in burning the carbon and hydrogen elements of the metabolism. They recognized, however, that this was a false method, and stated that they should employ the calorific value of fat, starch, and proteid, less the urea, since they recognized that urea was capable of undergoing combustion with liberation of heat.

In 1860 Voit[2] brought a Thomson calorimeter with him from London to Munich. After Frankland's determination of the heat value of the various foodstuffs and urea Voit[3] prepared a table in 1866 for use in his lectures showing that the metabolism of the fasting man experimented on by Pettenkofer and Voit indicated the production of 2.25 million small calories, while the metabolism on a medium diet was 2.40 million calories.

In 1873 Pettenkofer and Voit[4] calculated that 100 grams of fat were the physiological equivalent of 175 grams of starch. Liebig at that time had suggested that the amount of these substances which could be burned by a man was proportional to the oxygen supply.

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[1] Bischoff and Voit: "Die Gesetze der Ernährung des Fleischfressers," 1860, p. 43.

[2] Voit: "Münchener medizinische Wochenschrift," 1902, Bd. xlix, p. 233

[3] Voit: *Loc. cit.*

[4] Pettenkofer and Voit: "Zeitschrift für Biologie," 1873, Bd. ix, p. 534.

Voit, not content with his results, suggested to Schürmann in 1878–79 that he carry on experiments to see in what way carbohydrates and fat were interchangeable in nutrition. Schürmann died before the work was completed and the investigation was continued by Rubner. The isodynamic law, which showed that the foodstuffs replaced each other in accordance with their heat-producing value, was the result.

After Stohmann[1] published his research on the calorific value of foods, urea, etc., Voit commenced the construction of a calorimeter for the measurement of the heat eliminated from the body of a man whose metabolism was simultaneously determined. The results obtained by the use of this machine have never been published.

Rubner[2] in Voit's laboratory during this same period was making a series of valuable calorimetric determinations. The heat value to the body of burning starch and fat were obviously the same as that determined in the calorimeter, since in both cases the same end-products, carbon dioxid and water, resulted. The heat value of proteid in the calorimeter was different from its fuel value to the body, since the end-products were different in the two cases. When proteid burns in the body, the products of its metabolism are lost in three different ways—through the respiration, urine, and feces. The last two contain latent heat lost to the body, which must be deducted from the heat value of proteid determined calorimetrically.

The custom of Stohmann and previous authorities had been to deduct the heat value of urea from the heat value of proteid, in order to obtain the actual physiological or fuel value of proteid for the organism. But in the earliest experiments of Pettenkofer and Voit[3] it was recognized that in starvation urine, and in urines after the ingestion of meat, there was a much larger output of carbon in the urine than corresponded to the quantity

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[1] Stohmann: "Journal für praktische Chemie," 1885, Bd. xxxi, p. 273, and earlier papers.

[2] Rubner: "Zeitschrift für Biologie," 1885, Bd. xxi, pp. 250 and 337.

[3] Pettenkofer and Voit: *Ibid.*, 1866, Bd. ii, p. 471.

of urea present. The ratio of nitrogen to carbon was nearly constant in the urine when the conditions of feeding were similar. If urea alone were present, Rubner estimated there would be 0.429 grams of C to 1 of N or an N : C = 1 : 0.429. In starvation the urine contains extractive nitrogen (creatinin, uric acid, etc., having relatively more carbon than urea) which has been derived from the breaking down of tissue proteid, and the ratio is N : C = 1 : 0.728. When meat was ingested the fact that the food contained these extractives made the N : C ratio 0.610. And even after six days' ingestion of meat washed free from extractives the urine of the seventh and eighth days still showed an elimination of carbon other than that due to urea, as was indicated by the ratio 0.532. Therefore, from the metabolism following the ingestion of the proteids of washed meat small amounts of carbon compounds other than urea are eliminated in the urine.

Rubner saw that it was the heat value of the urinary constituents themselves which had to be subtracted from the heat value of proteid if the fuel value of proteid to the body was to be determined.

The following table shows Rubner's results after burning the dry urine:

CALORIC VALUE OF URINE.

Material Burned.	N : C.	Calories from 1 Gram.	Calorific Value of 1 Gram N.
Urea	0.429	2.523	5.41
Urine after feeding proteid	0.532	2.706	5.69
Urine after feeding meat	0.610	2.954	7.46
Urine in starvation	0.728	3.101	8.49

It was not alone necessary to know the heat value of the urine excreted, but also that of the feces. Rubner found that after giving 100 parts of dry muscle containing 5.5 grams of ash there was an elimination of 38.2 grams of the organic part in the urine and 2.7 grams in the feces. The following table represents this division of material in the excreta:

	C.	H.	N.	O.
Composition of 100 parts dry muscle	50.5	7.6	15.4	20.97
Urine contains 38.2 parts	9.63	2.52	15.16	10.9
Feces contain 2.7 parts	1.67	0.25	0.24	0.54
Excreted in urine and feces	11.30	2.77	15.40	11.44
Balance for respiration	39.2	4.8		9.53

Rubner determined the amount of heat produced from 1 gram of ash-free feces after meat ingestion and found it to be 6.127 calories, while 1 gram of ash-free feces after proteid (washed meat) ingestion yielded 6.852 calories. The total calorific value of one gram of beef muscle when Rubner burned it in the calorimeter was 5.345 calories. He had now the principal data required to determine its heat value in the body. If from 100 grams of meat 2.7 grams appear as feces having a calorific value of 6.127 calories per gram, then there is here a loss of 6.127 × 2.7 = 16.83 calories. If from every 100 grams of meat containing 15.4 grams of nitrogen 15.16 grams of the latter appear in the urine and such urine produced by ingesting meat has a calorific value of 7.46 calories for every gram of nitrogen present, then the energy loss in the urine would be 7.46 × 15.16 = 112.94. For dry muscle substance we find therefore:

			Calories.
100 grams muscle			534.5
Waste	Urine	112.94	
	Feces	16.83	Total 129.77
Fuel value of 100 grams of dry muscle			404.73

From this value there must be a slight deduction for the heat present in the proteid in its colloidal state but lost on drying, and for the heat of solution necessary to dissolve urea and other urinary constituents. Rubner estimates these as:

Heat for the imbibition of proteid	2.688
Heat for solution of urea	1.989
	4.677

Subtracting 4.67 from 404.73 leaves 400.06 calories as the maximum of energy obtainable from 100 grams of the dried

solids of meat. The calorimeter shows a heat value of 534.5 calories for the same proteid. Of this, 400.06 calories, or 74.9 per cent., is available in the organism, while the remainder, or 25 per cent., goes to waste.

A further calculation shows that every gram of nitrogen in the urine and feces represents an elimination of heat from proteid metabolism equal to 25.98 calories. The heat value of proteid under the different physiological conditions was estimated by Rubner after the above fashion, and may thus be tabulated:

CALORIFIC VALUE OF PROTEID IN NUTRITION.

	Calories Yielded by Metabolism of 100 Grams of Proteid in the Body.	Heat Value of Proteid Metabolism Yielding 1 Gm. of N in the Excreta.
After proteid (washed meat) ingestion ...	442.4	26.66
After meat ingestion	400.05	25.94
Starvation	384.2	24.94

If we know the amount of nitrogen in the excreta we can calculate from these standard figures of Rubner the heat value of the proteid metabolism to the body. Rubner found that the heat value of 1 gram of pig's fat (lard) was 9.423 calories. Since this fat contains 76.5 per cent. of carbon, it could be calculated that for every gram of carbon eliminated in the respiration, which was the result of fat metabolism, 12.3 calories must have been liberated in the body. These figures enabled Rubner to calculate the amount of heat liberated by the fasting man of Pettenkofer and Voit, whose metabolism we have already discussed. The N excreted was multiplied by 24.94, and the fat carbon by 12.3 which gave the total heat value of the period:

Heat from proteid (11.33 Gm. N × 24.94 Cal.)	283
Heat from fat (169.95 C × 12.3 Cal.).......................	2091
Total heat value of the metabolism as calculated..........	2374

Rubner applied such calculations as these to the material at hand in the literature of the time, and discovered that the heat value of the metabolism of the resting individual was proportional to the area of his body. For example, a man in starvation, or on a medium diet, an infant at the breast, and a starving dog, were shown to give off similar quantities of heat per square meter of surface. To these Rubner subsequently added the results of his researches upon a dwarf. The following tables illustrate this point:

	Yield of Calories per Sq. M. Surface in 24 Hours.
Adult man in starvation	1134
Dog in starvation	1112
Adult man on a medium mixed diet	1189
Breast-fed infant	1221
Dwarf (weight = 6.6 Kg.) medium mixed diet	1231

This law, that the resting animal in starvation or on a medium diet gives off the same quantity of heat per square meter of surface, can be extended so that it applies to all warm-blooded animals. Thus E. Voit[1] has collected data for the following table:

		Calories.	
	Weight in Kg.	Per Kilo.	Per Sq. M. Surface.
Pig	128.0	19.1	1078
Man	64.3	32.1	1042
Dog	15.2	51.5	1039
Goose	3.5	66.7	967
Fowl	2.0	71.0	947
Mouse	0.018		1188

Rubner from his work on proteid considered that the heat value of 1 gram in an average mixed diet might well be placed at 4.1 calories. Of course, such a mixed diet would contain casein (4.4 cal.), the organic substance of meat (4.233 cal.), and vegetable proteids (3.96 cal.). The daily food allowance for animal proteid was put at 60 per cent., for vegetable proteid at 40 per cent., of the total proteid in the mixed dietary. For the value of neutral fats Stohmann's figures for olive oil, animal fat, and butter fat were averaged as follows:

Olive oil	9.384	Calories per Gm.
Animal fat	9.372	" " "
Butter fat	9.179	" "
Average	9.312	" " "

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[1] E. Voit: "Zeitschrift für Biologie," 1901, Bd. xli, p. 120.

For the heat value of one gram of fat in a mixed diet Rubner therefore adopted the value 9.3.

The following heat values have been found for carbohydrates:

	Stohmann.	Rubner.
Dextrose	3.692	3.755
Milk sugar	3.877	
Cane Sugar	3.959	4.001
Starch	4.116	

Considering the predominating importance of starch in the average diet, Rubner gave the value of 4.1 to the group of carbohydrates in the foods.

Rubner's "standard values" have been widely used throughout the world in determining the average fuel value of a mixed diet. They are:

1 gram of proteid	4.1 calories
1 gram of fat	9.3 calories
1 gram of carbohydrate	4.1 calories

Their accuracy has been lately verified by Rubner[1] in the most careful manner.

Atwater and Bryant[2] have sought to modify this standard value and offer the following in substitution:

1 gram of proteid	4.0 calories
1 gram of fat	8.9 calories
1 gram of carbohydrate	4.0 calories

Atwater[3] states that these figures are absolutely available in computing the average diet (results of 411 experiments). The difference between the two standards probably lies in the fact that Rubner gave comparatively pure foods, while the waste through the feces in Atwater's diets reduced the nutritive availability. Another difference lies in the fact that Atwater[4] uses as a small calorie the amount of heat necessary to raise 1 c.c. of

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[1] Rubner: "Zeitschrift für Biologie," Festschrift zu Voit, 1901, Bd. xlii, p. 261.

[2] Atwater and Bryant: "Report of the Storrs Agricultural Experiment Station," 1899, p. 110.

[3] Atwater: "Am. Journal of Physiology," 1904, vol. x; "Proceedings of the Am. Physiol. Society," p. xxx.

[4] Atwater and Rosa: U. S. Dept. of Agriculture, Bulletin 63, 1899, p. 55.

water from a temperature of 19.5° to 20.5° instead of from 0° to 1°, the unit ordinarily employed.

Rubner,[1] still working in the Munich laboratory, showed that if the diet were increased from a medium to an abundant amount, the metabolism as indicated by the heat production rose. This *dynamic action* resulting from the excessive ingestion of a foodstuff was greatest with proteid, less after fat, and scarcely at all after carbohydrates.

Finally Rubner, in his own laboratory at Marburg, evolved an animal calorimeter which could accurately measure the amount of heat a dog produced in twenty-four hours. The dog was placed within the chamber of the calorimeter, and this chamber was attached to a respiration apparatus, so that the metabolism could be calculated according to the method of Pettenkofer and Voit. From the metabolism the heat production could be estimated. The results were a triumphant demonstration of the truth of the law of the conservation of energy. The amount of heat that Rubner[2] calculated should have been derived from the metabolism of the dog during the day spent in the calorimeter was the amount actually given off by the dog to the calorimeter. The metabolism, the cause of the motions of life, was the source of the heat-loss of the body. The results achieved constitute a final verification of the methods of calculating the total metabolism originated by Pettenkofer and Voit.

An epitome of Rubner's experiments is here presented:

COMPARISON OF ESTIMATED HEAT FROM METABOLISM WITH HEAT ACTUALLY PRODUCED.

FOOD.	NUMBER OF DAYS.	HEAT CALO. FROM METABOLISM.	HEAT DIRECTLY DETERMINED.	DIFFERENCE IN PERCENTAGE.
Starvation	5	1296.3	1305.2	—1.42
	2	1091.2	1056.6	
Fat	5	1510.1	1498.3	—0.97
Meat and fat	8	2492.4	2488.0	
	12	3985.4	3958.4	
Meat	6	2249.8	2276.9	—0.42
	7	4780.8	4769.3	+0.43

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[1] Rubner: "Sitzungsberichte der bayer. Akademie," 1885, p. 454.

[2] Rubner: "Zeitschrift für Biologie," 1893, Bd. xxx, p. 73.

Following Rubner, Atwater, at one time a pupil of Voit, with the aid of Rosa, the physicist, has constructed a large calorimeter capable of measuring to a nicety the amount of heat given off by a man living in it. This apparatus has confirmed Rubner's experiments and has shown that the energy expended by a man in doing any work, such as bicycle-riding, is exactly equal to the energy set free by metabolism in the body. *Ex nihilo nihil fit.*

This apparatus was the product of many years of labor and its cost was borne by the United States Government. Armsby has completed a similar one for use with cattle, for the Agricultural Station of the State of Pennsylvania. These elaborate and costly devices prove and confirm the general laws of metabolism in the body, through a knowledge of which alone proper systems of nutrition for people under various conditions may be devised. The American Indian when first shown a watch thought it was alive. We, on the other hand, have come to look upon the living as a machine. Like the moving locomotive, we burn more if we are to attain a faster speed, or if we are to keep all parts warm in the winter's cold, and a part of the fuel may be wasted as heat. In both cases the motion and the heat are derived from the power in the fuel. The casual observer sees the moving train, but the expert engineer alone knows how and why the wheels go around. The physiologist busies himself answering the similar how and why regarding the mechanism of living things.

Before taking up the details of the work, we may copy the last general pronouncement of Voit[1] upon the subject of metabolism. It reads:

"The unknown causes of metabolism are found in the cells of the organism. The mass of these cells and their power to decompose materials determine the metabolism. It is absolutely proved that proteid fed to the cells is the easiest of all the foodstuffs to be destroyed, next carbohydrates, and lastly fat. The metabolism continues in the cells until their power to

[1] Voit: "Münchener medizinische Wochenschrift," 1902, Bd. xlix, p. 233.

metabolize is exhausted. All kinds of influences may act upon the cells to modify their ability to metabolize, some increasing it or others decreasing it. To the former category belong muscular work, cold (in warm-blooded animals), abundant food, and warming the cells. To the latter, cooling the cells, certain poisons, etc.

"In speaking of the power of the cells to metabolize, I have not meant thereby, as may be seen from all my writings, that the cells must always use energy in order to metabolize, but rather I have understood thereby the sum of the unknown causes of the metabolic ability of the cells—as one speaks of the fermentative 'power' of yeast cells.

"The metabolism of the different foodstuffs varies with the quality and quantity of the food. Proteid alone may burn, or little proteid and much carbohydrates and fat. I have determined the amount of the metabolism of the various foodstuffs under the most varied conditions. All the functions of metabolism are derived from the processes in the cells. In a given condition of the cells, available proteid may be used exclusively if enough be furnished them. If the power of the cells to metabolize is not exhausted by the proteid furnished, then carbohydrates and fats are destroyed up to the limit of the ability of the cells to do so.

"From this use of materials arise physical results, such as work, heat, and electricity, which we can express in heat units. This is the power derived from metabolism.

"It is possible to approach the subject in the reverse order, that is, to study the energy production (Kraftwechsel) and to draw conclusions regarding the metabolism (Stoffwechsel). It is perfectly possible to say that the requirement of energy in the body or the production of the heat necessary to cover heat loss, or for energy to do work, are controlling factors over the metabolism; since on cooling the body or on working correspondingly more matter is destroyed. But one must not conclude that the loss of body heat or muscular work are the immediate causes of this increased metabolism. The causes lie in the peculiar conditions of the organism, and muscle work and loss of heat are merely factors acting favorably upon those causes, raising the power of the cells to metabolize. In virtue of this more is destroyed, and secondarily the power to work and increased heat production is afforded.

"The requirement for energy cannot possibly be the cause of metabolism, any more than the requirement for gold will put it in one's pocket. Hence the production of energy has a very definite upper limit, which is afforded by the ability of the cells to metabolize. If the cells will metabolize no more, then further increase of work ceases even in the presence of direst necessity; and this is also the case with the heat production, even though it were very necessary, and we were likely to freeze.

"I therefore maintain my 'older' point of view, that of pure metabolism, in order to explain the phenomena of nutrition. I am convinced that it is the right way, and that the clearest and most unifying development will be possible as one investigates what substances are destroyed under different circumstances, such as work, and loss of heat, and how much of the different materials must be fed to maintain the body in condition."

CHAPTER II.

THE FECES.

In the historical introduction of the preceding chapter it has been shown that the nitrogen of the urine and feces can be made a measure for the determination of proteid metabolism. It is easy to comprehend that urinary constituents, such as urea, uric acid, the purin bases, creatinin, etc., are derived from the metabolism of flesh in the body, whether the flesh be the body's own or that of an animal fed to it. But the intestinal canal where the feces are formed is a long tube open at both ends, through which may pass the nitrogen gas of the air swallowed and indigestible substances such as hair, tacks, etc. In diarrhea the curds of milk, pieces of undigested meat or bread, and large quantities of fat are in evidence. These common observations would seem to justify the popular supposition that normal feces are made up of the undigested residues of the foodstuffs. In truth, however, this is very far from the fact. The feces are chiefly the unabsorbed residues of intestinal excretions.

The collection of the feces for a given period of nutrition is more difficult than the collection of the urine. The urine may be collected every two hours and may fairly represent the proteid metabolism of the time, but the feces are normally passed but once a day by a man on a mixed diet, and only once in five days by a dog fed with meat. Furthermore, particles fed to a man are not passed in his feces for two or three days. The feces formed during a certain digestive period might therefore leave the body two or three days after the urine was drawn from the bladder. To obtain clear results Voit fed a dog with 60 grams of bones in a preliminary diet eighteen hours before the regular feeding began. These bones yielded a whitish mark in the fecal excretion. All feces subsequent to the mark were attributed to the diet used in the experiment. At the conclusion of the experiment a second diet containing bones was given. The whitish excrement formed from this indicated the end of the feces of the period. For the same purpose Rubner [1] gave milk (2 liters) to a man, the last portion of the milk being taken eighteen hours before the commencement of a period of feeding. The milk feces give a distinct whitish dividing line. A teaspoonful of lampblack may also be readily made use of in man and in animals. Cremer [2] uses freshly precipitated silicic acid (10 to 25 grams mixed with 40 to 100 grams fat) instead of bones. This gives excellent results, as it avoids the gelatin nitrogen in the bones, and is of great advantage if the calcium or other ash constituents of the feces are to be determined.

In the fundamental experiments Voit found that a fasting dog weighing 30 kilograms excreted 1.88 grams of dry fecal matter per day, containing 0.15 gram of nitrogen. Evidently these starvation feces are not derived from the food, but must be derived from the matter passed from the body into the intestinal canal. An analogous condition is found in the intestinal tract of the new-born infant. The meconium consists principally of the unabsorbed residues of the bile, of glycocholic, taurocholic, and fellic acids, of cholesterin and lecithin, colored by bilirubin or biliverdin. The absence both of putrefaction and the acid of the gastric juice prevents the breaking up and reabsorption of many of these substances, processes which occur soon after birth. The fasting dog of 30 kilograms, mentioned above, excreted 1.88 grams of dry feces, but a fasting dog of 20.3 kilograms may yield 4.3 grams of dry bile solids in twenty-four hours.[3] The ordinary starvation feces therefore cannot consist of the total of the excretions from the body into the digestive tract, but rather their unabsorbed remainder.

When meat was given, Bischoff and Voit [4] found that the

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[1] Rubner: "Zeitschrift für Biologie," 1879, Bd. xv, p. 119.
[2] Cremer: *Ibid.*, 1897, Bd. xxxv, p. 391.
[3] Voit: *Ibid.*, 1894, Bd. xxx, p. 548.
[4] Bischoff and Voit: "Die Ernährung des Fleischfressers," 1860, p. 291.

production of feces was not proportional to the amount of meat. The following table illustrates the average amount of dry feces produced by a dog weighing 35 kilograms after feeding different quantities of meat:

Meat in Grams.	Dry Feces.
500	10.7
1800	11.2
2500	11.93

The feces had the same pitch-black color as starvation feces and were similar to the 2 grams of feces which would have been produced by the same dog had he been starving. No muscle fibers and no proteid could be detected. It seemed clear that the meat feces differed from the starvation feces mainly in quantity, and that this quantity was larger because the secretions into the intestines had been stimulated by the passing food.

Fat ingested with the meat in moderate quantities had no influence on the feces. Nor had sugar, unless its fermentation produced diarrhea. Bread somewhat increased the volume of the feces, which contained some undigested starch. Here an irritation of the intestinal canal by the bread produced a larger excretion into the intestine.

The source of the feces was further investigated by Fritz Voit,[1] who separated a loop of the intestine about a third of a meter long from the rest of the intestine of a starving dog. Both ends of the loop were tied and the loop remained in the abdomen in connection with its normal nerve and blood supply. The two ends of the remaining portion were resected. After a few days food could be given and the normal excretion of feces took place. After three weeks the animal was killed. It was found that the isolated loop contained a thick, fecal-looking mass. It was found that the dry solids of this mass contained the same percentage of nitrogen as did the feces passed by the dog during the three weeks of the experiment. It was also calculated that the amount of nitrogen excreted through the wall of the intestinal loop per square meter of its surface was

[1] F. Voit: "Zeitschrift für Biologie," 1892, Bd. xxix, p. 325.

nearly the same per unit of area as the amount of nitrogen in the feces when spread over the surface of the whole of the resected intestine. The following table shows this:

	Percentage of N in the Dry Substance.		Grams N from 1 Sq. M. in 24 Hours.	
	Feces.	Content of Loop.	Feces.	Content of Loop.
Dog I	5.62	5.32	0.28	0.22
Dog III	5.27	6.88	0.25	0.32

The loop contained fat and fatty acids in greater quantity than is normally found in feces, which may indicate a usual reabsorption of these substances.

Fritz Voit has therefore shown that the excretion of substances from an isolated loop of the intestine produces a mass of a similar constitution and of nitrogen output equal to that in the normal resected intestine of the same animal through which meat and fat were passing. He therefore concludes that the feces are derived principally from the substances excreted through the wall of the intestine. The nitrogen so excreted is as much to be considered a product of proteid metabolism as is the nitrogen of urea. It is regretable that very little is known regarding the chemistry of these nitrogenous compounds excreted into the intestine.

It has been seen that the feeding of simple foodstuffs, such as meat, fat, and sugar, scarcely influenced the composition of the feces in the dog. In herbivora we pass to another extreme. Here vast amounts of cellulose are eaten, a great part of which is never digested, but even after long retention in the capacious intestinal tract is passed in the feces. After giving an ordinary fodder to a cow, as much nitrogen may be passed in the feces as in the urine. Under such conditions as these, the very voluminous feces evidently do consist largely of the undigested residues of the fodder.

Concerning the fecal production in man, it has been found that Cetti[1] excreted 3.8 grams of dry fecal solids per day during a fast of ten days, Breithaupt 2 grams, and a medical student[2] 2.2 grams, less in reality than would a dog of similar size.

Rieder[3] fed a man on a diet containing starch, sugar, and lard from which a cake was baked. The food contained no nitrogen, but the fecal excretion was 0.54, 0.87, and 0.78 gram of nitrogen per day, contrasting with 0.316 gram from Cetti, 0.113 from Breithaupt, and 0.13 from a medical student during fasting. The food, even though it contains no proteid, stimulates the fecal production.

It has been stated that Voit early noticed the occurrence of starch particles in the feces. A large number of experiments have been made to test the digestibility of the various vegetables and cereals. Rubner[4] fed an able-bodied soldier on 3078 grams of variously cooked potatoes daily and found pieces of potatoes in the feces. He notes that an inhabitant of Ireland will eat 4500 grams of potatoes a day. Friederich Müller[5] writes that after feeding a large quantity of bread, the feces may have practically the same composition as bread.

The better understanding of this question of the "digestibility" of the carbohydrates has come through the work of Prausnitz[6] and his pupils, Moeller and Kermauer. Moeller found that no starch appeared in the feces after feeding well-cooked white, rye, and graham bread, rice or potatoes (even when fed in pieces) or legumes when they were prepared in the form of purée. Legumes not in the form of purée, such as string beans eaten as salad, may resist the action of the digestive juices so that the starch contents of the cell is untouched, and the vegetable cells appear in the feces. These facts explain the appearance of bread in the feces if the bread be badly cooked, or if

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[1] Lehmann, Müller, I. Munk, Senator, Zuntz: "Virchow's Archiv," 1893, Bd. cxxxi. Suppl. Heft.

[2] Johansson, Landergren, Sonden, Tigerstedt: "Skandin. Archiv für Physiologie," 1896, Bd. vii, p. 29.

[3] Rieder: "Zeitschrift für Biologie," 1884, Bd. xx, p. 378.

[4] Rubner: *Ibid.*, 1879, Bd. xv, p. 146.

[5] Fr. Müller: *Ibid.*, 1884, Bd. xx, p. 375.

[6] Prausnitz: *Ibid.*, 1897, Bd. xxxv, p. 335.

such a "heavy" bread as pumpernickel be eaten. The imperfectly cooked bread contains starch granules whose coverings are impermeable to the digestive juices, as are also many of those in the unbolted rye of pumpernickel.

Prausnitz finds that if a man be put on a rice diet and then meat be substituted for most of the rice, the composition of the feces does not vary with the diet. Such feces he calls *normal feces*. They may contain a negligible quantity of fibers of meat (Kermauer) or of cellulose from the rice.

The feces of six persons placed alternately on meat and rice diets yielded normal feces, the percentage composition of whose dry solids was as follows:

COMPOSITION OF FECES ON DIFFERENT DIETS.

No.	Person.	Principal Food	N %.	Ether Extract %.	Ash %.
1	H.	Rice	8.83	12.43	15.37
2	H.	Meat	8.75	15.96	14.74
3	M.	Rice	8.37	18.23	11.05
4	M.	Meat	9.16	16.04	12.22
5	W. P.	Rice	8.59	15.89	12.58
6	W. P.	Meat	8.48	17.52	13.13
7	J. Pa.	Rice	8.25		14.47
8	J. Pa.	Meat	8.16		15.20
9	F. Pi.	Rice	8.70		16.09
10	F. Pi.	Meat	9.05		15.14
11	Vegetarian.	Rice	8.78	18.64	12.01
		Average,	8.65	16.39	13.82

It is seen from this that whether the food solids contain 1.5 per cent. N, as in rice, or ten times that, as in meat, the composition of the feces remains uninfluenced. Normal feces result from the eating of any food which is completely digested and absorbed. In all such cases these feces have the same composition and are derived from the intestinal wall. It is therefore not astonishing that a vegetarian of many years' standing produced the same kind of feces when fed on rice as did the other men. The same quality of feces has been obtained after giving good bread.

In this connection it is interesting to note that the heat value of one gram of human feces is very constant whether the person is on a meat diet or a medium mixed diet. Rubner[1] gives the value of one gram of organic matter in the feces of a man on a meat diet at 6.403 cal., while on a mixed diet one gram varies between 6.061 and 6.357 cal. The average fuel value of feces is therefore 6.2 calories per gram of dry organic substance, and this changes only when there is a poor utilization of the food.[2] According to Lorisch,[3] one may calculate the approximate heat value of feces by reckoning the nitrogen therein as proteid, and multiplying the "proteid," "fat" and carbohydrate present, by their usual heat value. The sum of these is said to give a rough estimate of the calorific loss through the feces.

After eating pumpernickel, bad bread or string beans the waste of undigested residues of these substances may appear in the feces, changing its composition and lowering its percentage of nitrogen content.

In general, Prausnitz finds no difference between the digestibility and absorbability of animal and vegetable foods. Meat, rice, and bread from fine flour are all digested and absorbed. The ordinary feces indicate whether a given food is a small or a great feces builder, not how much or how little food has been used for the organism.

The value in such foods as cabbage, string beans, cauliflower and the like lies, aside from their flavor, in the fact that their indigestible waste may enhance peristalsis in the intestine. Their food value is small, and if given to those with weak digestions, is dubious.

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[1] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 35.

[2] Rubner: Leyden's "Handbuch der Ernährungstherapie," 1903, p. 32.

[3] Lorisch: "Zeitschrift für physiologische Chemie," 1904, Bd. xli, p. 308.

CHAPTER III.

STARVATION.

Starvation, or hunger, is the deprivation of any or all the elements necessary to the nutrition of an organism. Thus when carbohydrates and fats only are eaten, proteid hunger ensues. If the body is deprived of water or of calcium, thirst and calcium hunger, as the case may be, follow. Complete starvation occurs when all the required elements are inadequate. A fasting dog to whom no food or drink is offered does not undergo starvation in this sense, for a dog does not sweat through his skin, as is the case in man, and the metabolized tissue furnishes enough water for the urine and respiration. There is also no water hunger in a dog when meat is ingested, for the meat contains enough water to dissolve the end-products of its metabolism in the urine.

A true picture of water hunger is presented by Straub,[1] who gave a dog dry meat powder mixed with fat. Under these circumstances water is withdrawn from the tissues to dissolve the urea formed. He found that muscles may lose 20 per cent. of their water content without pathological manifestations, although withdrawal of water somewhat increased the proteid metabolism. The experiment could not be carried to the point of death from thirst, for after a few days the food was regularly vomited, on account of the decreased flow of the digestive secretions and an altered condition of the intestinal canal. The non-absorption of the meat powder threw the body on the resources of its own tissue, and this form of starvation, as has been shown, does not constitute water hunger.

Rubner [2] finds that starving pigeons die of thirst in four to

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[1] Straub: "Zeitschrift für Biologie," 1899, Bd. xxxviii, p. 537.

[2] Rubner: Leyden's "Handbuch der Ernährungstherapie," 1903, p. 53.

five days, while those allowed only water live twelve days. Water hunger is therefore more quickly fatal than starvation when water is allowed. Under the usual conditions of so-called starvation experiments water is freely allowed, so that water hunger does not enter as a factor into the following discussion.

If water be available, the organism obtains the energy necessary for its continued existence from the destruction of its own store of proteid and fat. After a variable length of time the organism succumbs. Exposure to cold greatly hastens the end. What is ordinarily called death from starvation is often really death from exposure.

Succi has fasted several times for thirty days. Dr. Tanner, an American physician, for forty days; and Merlotti in Paris for fifty days. Succi took laudanum in considerable quantity to stay the pain in his stomach, while Merlotti took only water.[1] The effect of fasting on the spirits of the faster varies with the individual. Usually there is a loss of buoyancy of spirit, a decreased desire to work, and a decrease in the actual power to work. Succi, however, was capable of considerable exertion, such as walking and riding, without ill effects. A dog does not manifest the same depression as is seen in man. Dogs may be starved several days before they are run in a hunt. The longest fast on record is that of Kumagawa's[2] dog, who died on the ninety-eighth day. This dog was reduced in weight from 17 to 5.96 kilograms, a loss of 65 per cent.

The day to day history of the starving organism must now be considered.

In the first days the amount of proteid metabolized depends upon the two factors, the glycogen content of the individual and the quantity of proteid ingested before the starvation period. The influence of the first factor was shown by Prausnitz.[3] Fifteen individuals (mostly medical students who were taking

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[1] Luciani: "Das Hungern," 1890, p. 28.

[2] Kumagawa and Hayashi: "Archiv für Physiologie," 1898, p. 431.

[3] Prausnitz: "Zeitschrift für Biologie," 1892, Bd. xxix, p. 151.

a course of instruction in the laboratory) fasted for sixty hours. The first day's urine was collected beginning after twelve hours of fasting. The second day's urine contained in twelve cases more nitrogen than that of the first day of starvation. The lower proteid destruction on the first starvation day must have been due to the continued use of sugar from the glycogen supply. It is known that the combustion of sugar considerably reduces the proteid metabolism, so the second day and not the first of starvation should be taken as the basis of the fasting proteid metabolism.

The second factor, or the influence of the previous meat ingestion, is especially dominant in dogs. Voit[1] fed a dog weighing 35 kg. with different quantities of meat and noticed the effect on urea elimination during subsequent starvation. The results were as follows:

INFLUENCE OF PREVIOUS DIET ON UREA ELIMINATION IN STARVATION.

	Grams of Urea Excreted During Starvation Following Various Diets.				
	Meat, 2500 G.	Meat, 1800 G.; Fat, 250 G.	Meat, 1500 G.	Meat, 1500 G.	Bread.
Last food day	180.8	130.0	110.8	110.8	24.7
1st fasting day	60.1	37.5	29.7	26.5	19.6
2d “ “	24.9	23.3	18.2	18.6	15.6
3d “ “	19.1	16.7	17.5	15.7	14.9
4th “ “	17.3	14.8	14.9	14.9	13.2
5th “ “	12.3	12.6	14.2	14.8	12.7
6th “ “	13.3	12.8	13.0	12.8	13.0
7th “ “	12.5	12.0	12.1	12.9	...
8th “ “	10.1	...	12.9	12.1	...
9th “ “	...	...	...	11.9	...
10th “ “	...	...	...	11.4	...

It is evident from this that on the sixth day of starvation the urea elimination was the same in all cases, or about thirteen grams. Voit, however, assumed a fasting minimum of twelve grams of urea per day. He deducted the twelve grams from

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[1] Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 307.

what he had found for the first days and obtained the grams of urea which were derived from the previous food, as follows:

UREA ELIMINATION IN STARVATION ATTRIBUTABLE TO PREVIOUS DIET.

	Meat, 2500 G.	Meat, 1800 G.; Fat, 250 G.	Meat, 1500 G.	Meat, 1500 G.	Bread.
(Last food day)	(168.8)	(118.0)	(98.8)	(98.8)	(12.7)
1st fasting day	48.1	25.5	17.7	14.5	7.6
2d " "	12.9	11.3	6.2	6.6	3.6
3d " "	7.1	4.7	5.5	3.7	2.9
4th " "	5.3	2.8	2.9	2.9	1.2
5th " "	0.3	0.6	2.2	2.8	0.7

The amount of extra proteid metabolism is seen from the above to be directly dependent on the previous feeding, a common level being reached in all cases on the fifth day of fasting.

These experiments led Voit to differentiate between "circulating proteid," which could be absorbed, carried to the tissues, and burned, and "organized proteid," which was the more resistant living proteid of the tissues themselves. Voit[1] stated that in metabolism the lifeless proteid furnished to the cells by the blood was used in preference to the living organized tissue proteid. He quoted Landois's experiments, which show that after producing an artificial plethora through injection of blood, the serum proteids are readily burned and their nitrogen eliminated in the urine, while the red blood-cells containing the organized proteid are only slowly destroyed. If serum alone be transfused its proteid is rapidly destroyed.[2]

Even in starvation there is evidence of "circulating proteid" as food for the tissues. Thus Miescher showed that the salmon, after entering the Rhine from the sea, virtually starves. Yet the genital organs of both male and female greatly develop, this being at the expense of the muscles, which may lose 55 per cent. of their weight. This proteid must have been carried to

[1] Voit: "Handbuch der Ernährung," 1882, p. 300.

[2] Forster: "Zeitschrift für Biologie," 1875, Bd. xi, p. 496.

the various parts of the body in the circulating blood-stream. Miescher finds no indication of any destruction of muscle fibers in this process of emaciation. It is interesting in this connection to note that A. R. Mandel[1] has been able at a pressure of 300 to 350 atmospheres acting on lean meat seventy-two hours old to press a fluid containing 44 per cent. of the proteid present in the fibers, and this without visible change from the normal histological appearance of the muscle.

It seems quite possible that in ordinary starvation proteid from the muscle and other tissue passes to the blood and is carried to all the organs as circulating proteid for the nutrition of their cells.

In modern critical consideration of the "circulating proteid" it must be borne in mind that the amino products resulting from proteid digestion are probably largely metabolized as such, and are only in part regenerated into proteid within the organism (page 291). Since the composition of the blood-plasma is practically the same in starvation as after large digestion of meat (page 70), it is evident that the storage of such regenerated proteid must be effected elsewhere than in the blood (page 159).

Another thought is that when tissue proteid becomes circulating proteid in the cited case of the salmon, modern theory would assume its cleavage into amino acids previous to its regeneration into the tissue proteid of the genital organs. Thus Kossel[2] estimates that a salmon weighing 9 kg. deposits at breeding-time in his testicles 27 grams of salmin containing 22.8 grams of arginin. Kossel calculates that metabolism of muscle proteid during this time yields ample arginin to form the new salmin.

Whatever misconstruction has been placed on Voit's term "circulating proteid," discussion of the subject has served to emphasize the distinction between the behavior of living tissue proteid and the lifeless proteid (or proteolytic cleavage products) of the nourishing fluid.

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[1] Mandel: Unpublished work from the Munich Clinic of Prof. Fr. Müller.

[2] Kossel: "Biochemisches Centralblatt," 1906, Bd. v, p. 33.

This point is furthermore strongly illustrated by the behavior of gelatin. Voit has demonstrated that although gelatin can never be converted into tissue proteid nor be retained in the body, its ingestion may in part prevent the combustion of the living proteid tissue of the body (page 102).

The amount of proteid metabolized by a starving animal in good condition bears quite a constant relationship to the total metabolism involved. Even in different animals this constancy is observed. E. Voit[1] calls attention to the fact that the nitrogen elimination is not dependent on the weight of the animal, since a pig of 115 kilos produces 0.11 gram per kilo, whereas a guinea-pig weighing but 0.6 kilo eliminates 0.65 gram of nitrogen per kilo, or ten times as much. However, a comparison of the percentage of the total energy derived from proteid in fasting animals in good condition (*i. e.*, with considerable fat) varies within much narrower limits — between 7.3 and 16.5 per cent. This is shown in the following table:

NITROGEN METABOLISM OF DIFFERENT ANIMALS IN STARVATION.

Animal.	Weight in Kg.	N Elimination.			Percentage of Calories from Proteid.
		Total.	Per Kg.	Per Sq. M. Surface.	
Pig	115.0	6.8	0.06	3.2	7.3
Man	63.7	12.6	0.20	6.4	15.6
Dog I	28.6	5.1	0.18	5.2	13.2
Dog II	18.7	3.8	0.20	4.6	10.7
Dog III	7.2	2.2	0.30	5.2	13.5
Rabbit	2.7	1.2	0.46	4.8	16.5
Goose	3.3	0.8	0.23	3.3	7.4
Fowl	2.1	0.7	0.34	4.2	10.0
Guinea-pig	0.6	0.4	0.65	4.2	10.8

It is evident from the above that an average of 90 per cent. of the energy of the fasting metabolism may be supplied by non-proteid material. This material is fat (see page 26).

If a fasting organism be kept at the same temperature and under the same conditions as regards the performance of

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[1] E. Voit: "Zeitschrift für Biologie," 1901, Bd. xli, p. 188.

external work, the metabolism is remarkably even from day to day.

Hanriot and Richet[1] showed the even absorption of oxygen and elimination of carbon dioxid during the early days of fasting in man, as is illustrated in this table:

	Liters O_2 per Hour.	Liters CO_2 per Hour.
After 17 hours' fast	17.4	15.3
" 24 " "	16.85	14.15
" 29 " "	16.05	14.30
" 46 " "	16.9	14.35

Later Lehmann and Zuntz[2] made some experiments on the professional faster Cetti. They analyzed his urine and feces, and also obtained two samples of the carbon dioxid eliminated between 10 and 11 A. M., each period of collection lasting from ten to fourteen minutes. In other words, the carbon dioxid output was determined for only twenty to twenty-six minutes daily. From these data the total day's metabolism was calculated. This method is only approximately correct, but it is more accurate in the even metabolism of starvation than after foods have been ingested. In this method the lower metabolism during the night is not taken into consideration.

The investigation of the metabolism of Cetti during a ten days' fast was as follows:

METABOLISM OF CETTI IN STARVATION.

Fasting Days.	Proteid.	Fat.	Calories from Proteid.	Calories from Fat.	Calories, Total.	Calories per Kilo.
1 to 4	85.88	136.72	329.8	1288.2	1618	29.00
5 to 6	69.58	131.30	267.3	1237.4	1504	28.38
7 to 8	66.30	149.35	254.7	1407.3	1662	31.74
9 to 10	67.96	132.38	261.1	1247.4	1508	29.26

A very careful experiment on the metabolism of a fasting medical student twenty-six years old was made by Johansson,

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[1] Hanriot et Richet: "Comptes rendus de l'Academie des Sciences," 1888, Tome cvi, p. 496.

[2] Lehmann and Zuntz: "Arch. f. pathol. Anat.," 1893, vol. cxxxi, Suppl. p. 23.

Landergren, Sonden and Tigerstedt.[1] The man fasted five days, doing light work in the respiration apparatus. The metabolism during these days was determined. The excreta in grams were as follows:

METABOLISM OF J. A. IN STARVATION.

Day of Fasting.	N Elimination.			C Elimination.			
	Urine.	Feces.	Total.	Urine.	Feces.	Respiration.	Total.
1	12.04	0.13	12.17	8.0	1.1	188.5	197.6
2	12.72	0.13	12.84	8.3	1.1	179.4	188.8
3	13.48	0.13	13.61	9.9	1.1	172.2	183.2
4	13.56	0.13	13.69	10.3	1.1	169.4	180.8
5	11.34	0.13	11.47	9.3	1.1	165.8	176.2

The evenness of the carbon and nitrogen elimination is remarkable. From the above figures the following table of the general metabolism is made:

Day of Fasting.	Proteid.	Fat.	Calories from Proteid.	Calories from Fat.	Calories. Total.
1	76.1	206.1	303.5	1916.9	2220.4
2	80.3	191.6	320.5	1781.9	2102.4
3	85.1	181.2	339.4	1684.7	2024.1
4	85.6	177.6	341.4	1651.9	1992.3
5	71.7	181.2	286.1	1684.7	1970.8

Further calculation shows the following relations between the weight of the individual and the calorific production:

Day of Fasting.	Weight in Kilos.	Calories per Kilo.
1	66.99	33.15
2	65.71	32.00
3	64.88	31.20
4	63.99	31.13
5	63.13	31.23

On the fifth day of fasting it is seen that the individual burned 71.7 grams of proteid, 181.2 grams of fat, and produced

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[1] "Skandin. Archiv für Physiologie," 1896, Bd. vii, p. 54.

1971 calories, or 31.23 calories per kilogram of body substance. This is presumably the minimum compatible with ordinary life.

E. Voit[1] gives the following summary of the energy requirements during the early days of starvation in man:

GENERAL TABLE OF STARVATION METABOLISM IN MAN.

Day of Fast.	Weight.	Energy in Calories.			Author.
		Total.	Per Kg.	Per Sq.M. Surface.	
1	70.6	2359	33.4	1112	Pettenkofer and Voit.
1	70.4	2222	31.6	1060	Pettenkofer and Voit.
1 to 5	64.9	2071	31.9	1042	Tigerstedt.
1	59.5	1893	31.8	1012	Zuntz and Lehmann.
1 to 2	56.0	1773	31.7	985	Zuntz and Lehmann.

This minimal metabolism requirement of the fasting organism appears remarkably constant in different men. Not only is the total metabolism the same but also the amounts of proteid and fat which yield the energy are the same. This is shown by comparing the nitrogen excretion of the different fasters during the first days. These are as follows:

	Cetti.[2]	Breithaupt.[3]	Succi.[4]	J.A.[5]	Succi.[6]
1	13.55	10.01	13.81	12.17	17.00
2	12.59	9.92	11.03	12.85	11.20
3	13.12	13.29	13.86	13.61	10.55
4	12.39	12.78	12.80	13.69	10.80
5	10.70	10.95	12.84	11.47	11.19
6	10.10	9.88	10.12	.....	11.01

It is thus evident that if the organism has previously been well nourished, the fasting metabolism is remarkably even, about 13 per cent. of the total energy being derived from proteid and 87 per cent. from fat.

[1] Voit, E: "Zeitschrift für Biologie," 1901, Bd. xli, p. 114.

[2] Munk: "Arch. f. Path. Anat.," 1893, Bd. cxxxi, Suppl. p. 25.

[3] Munk: *Ibid.*, p. 68.

[4] Luciani: "Das Hungern," 1890.

[5] Johansson, Landergren, Sonden and Tigerstedt: "Skandin. Archiv. für Physiol.," 1896, Bd. vii, p. 54.

[6] E. and O. Freund: "Wiener klinische Rundschau," 1901, Bd. xv, p. 91.

During prolonged fasting the nitrogen output sinks much below the figures of the earlier days. Thus a woman twenty-four years old averaged 4.15 gm. from the thirteenth to the twenty-fifth day of fasting.[1] A girl nineteen years old whose esophagus had been occluded by drinking sulphuric acid excreted 2.8 grams of nitrogen on the sixteenth day of fasting.[2] An invalid of Tuczec's[3] averaged 4.25 grams of nitrogen between the fifteenth and twenty-first days. Under Luciani's observation, Succi excreted 4.08 grams on the twenty-ninth day, and under E. and O. Freund his nitrogen excretion was 2.82 grams on the twenty-first day. The latter authors say that after this there was a sudden rise in the amount of nitrogen and chlorin in the urine, suggesting the so-called *premortal rise*, which caused them to stop the experiment. About 3 grams of nitrogen in the urine or a daily destruction of 18.75 grams of proteid would seem to be the lowest extreme of proteid metabolism in the emaciated organism after a prolonged fast. The analyses by E. and O. Freund of Succi's urine during a fast of twenty-one days is the most complete record of the sort. The daily nitrogen excretion is given in grams below:

DAILY NITROGEN EXCRETION OF SUCCI IN STARVATION.

Day	N.	Day.	N.	Day.	N.
1	17.0	8	9.74	15	5.05
2	11.2	9	10.05	16	4.32
3	10.55	10	7.12	17	5.4
4	10.8	11	6.23	18	3.6
5	11.19	12	6.84	19	5.7
6	11.01	13	5.14	20	3.3
7	8.79	14	4.66	21	2.82

The nitrogen and total sulphur ran together in the urine in the proportion of 17.3 N: 1 S. Munk found the relation $\frac{N}{S}$ to be 14.7 in Breithaupt, and 15.1 in Cetti. The sulphur

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[1] Seegen: "Wiener Acad. Sitz. Ber.," Bd. xxxiii, 2 Abth.

[2] Schultzen: "Virchow's Archiv," 1863, p. 31.

[3] Tuczec: "Arch. für Psychiatrie," Bd. xv, p. 764.

is believed to be derived exclusively from the breaking down of proteid.

The nitrogen and total phosphoric acid (P_2O_5) in the urine are not found in the same relation as that in which they exist in meat (7.6:1), but there is a greater phosphoric acid excretion. This is also true of the calcium excretion. This greater excretion is due to the metabolism of the bones (Munk). E. and O. Freund found that the $\frac{N}{P_2O_5}$ fell from 5.7 on the first day of Succi's starvation to between 4.2 and 4.4 during the subsequent periods. Munk found this value to be 4.4 in Cetti during ten days and 5.1 in Breithaupt during six days.

A partial record of the work of E. and O. Freund on Succi is given below. Their analyses of the urine of the first, third, eleventh, and twenty-first days of starvation are in part reproduced.

COMPLETE URINARY ANALYSIS OF SUCCI ON FIRST, THIRD, ELEVENTH, AND TWENTY-FIRST STARVATION DAYS.

Day of Fasting.	1st.	3d.	11th.	21st.
Amt. urine, c.c	1435	575	378	235
Total N, grams	17.0	10.55	6.32	2.82
Urea N, grams	14.8	9.65	5.64	1.65
Uric acid N	0.29	0.20	0.075	0.046
Purin base N	0.13	0.064	0.042	0.034
Creatinin N	0.134	0.198	0.372	0.025
Ammonia N	0.43	0.144	....	0.10
Total S	3.2	1.3	0.8	....
Total P_2O_5	2.98	2.52	0.41	0.64
Cl	14.9	2.56	1.51	0.7
Ca	0.25	....	0.31	....
Mg	0.33	....	....	....

Examination of the above will show that whereas in the earlier days of the experiment the relationship between urea nitrogen and total nitrogen is the normal of about 85 per cent., during the last days it has fallen to 54 per cent. The balance of the total nitrogen not enumerated above is made up of constituents of unknown character. The Freunds attribute great significance to this distribution of nitrogen in the urine, which was noteworthy between the sixteenth and the twenty-first days. A similar ratio may exist in the urine of a man unaccustomed to exercise who does hard work.[1]

The relative ammonia excretion was apparently the same as normal. The purin bodies ran low. The chlorin excretion almost vanished, so great is the retentive power of the body for its sodium chlorid constituents. Of pathological substances, the urine contained acetone, diacetic acid, urobilin, and dextrose. The dextrose was too small in amount to be quantitatively determined.

A communication by Brugsch,[2] shows that the quantities of β-oxybutyric acid and acetone in the urine become very great in extreme hunger. The experiment was also on Succi, between the twenty-third and the thirtieth days of starvation and showed the following remarkable values:

ACETONURIA IN STARVATION (SUCCI).

Starvation Day.	N in Grams.	β-oxybutyric Acid in Grams.	Acetone in Grams.
23d	5.87	9.24	0.569
24th	6.41	8.43	0.410
25th	6.27	9.85	0.463
26th	6.18	5.28	0.569
27th	6.30	11.62	0.525
28th	4.43	6.99	0.339
29th	4.19	9.15	0.242
30th	8.42	13.60	0.115

The excretion of urea nitrogen ran between 54 and 70 per cent., and the ammonia nitrogen between 15.4 and 35.3 per cent. of the total nitrogen in the urine. The high ammonia neutralized the very considerable acidosis.

Albumin is also of frequent occurrence in the starvation urine of man and animals.

It has already been set forth that the general metabolism is extremely even in fasting, and it may be added that existing evidence shows the intermediary metabolism has a similar

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[1] Jackson: "Archives italiennes de Biologie," 1901, Tome xxxvi, p. 463.

[2] Brugsch: "Zeitschrift für ex. Pathologie und Therapie," 1905, Bd. i, p. 419.

character. Thus Stiles and Lusk[1] found in a fasting dog made diabetic with phlorhizin that whereas the quantity of nitrogen and sugar eliminated slowly fell, the relation between the two (the Dextrose : Nitrogen or D:N ratio) remained constant. This is shown in the following table:

CONSTANT RATIO BETWEEN DEXTROSE PRODUCTION AND N ELIMINATION IN STARVATION.

PERIOD.	D PER HOUR.	N PER HOUR.	D : N.
15 hours........................	2.61	0.735	3.56
6 “	...	0.720	...
3 “	...	0.683	...
12 “	2.39	0.666	3.60
3 “	2.51	0.687	3.65
6 “	...	0.670	...
3 “	2.36	0.643	3.66
11 “	2.32	0.642	3.62

The hour to hour sugar production from proteid is therefore even and constantly proportional to the proteid metabolism.

Parker and Lusk[2] showed that if benzoic acid be administered as lithium benzoate twice a day to a fasting rabbit the animal will combine it with the glycocoll of its metabolism in such quantity that the amount of the resulting hippuric acid bears a constant ratio to the total nitrogen elimination of the period. In other words, there is a constant production of glycocoll in the organism which is normally burned, but which in this case is combined with benzoic acid and eliminated in the urine. The formula representing the formation of hippuric acid is as follows:

$$\underset{\text{Benzoic Acid.}}{C_6H_5COOH} + \underset{\text{Glycocoll.}}{NH_2CH_2COOH} = \underset{\text{Hippuric Acid.}}{C_6H_5CO.NHCH_2COOH} + H_2O$$

The results of the experiment indicate a production of 3.98 grams of glycocoll from the metabolism of 100 grams of body proteid. The following table begins with the fifth fasting day and the second of benzoate feeding, and is as follows:

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[1] Stiles and Lusk: "American Journal of Physiology," 1903, vol. x, p. 77.

[2] Parker and Lusk: *Ibid.*, 1900, vol. iii, p. 478.

CONSTANT RATIO BETWEEN GLYCOCOLL PRODUCTION AND N ELIMINATION IN STARVATION.

	N.	Hippuric Acid.	Ratio Hippuric Acid (or Glycocoll) N: Total N.
5th day of fast	0.990	0.7060	1:18.0
6th " " "	1.087	0.6340	1:21.6
7th " " "	0.775	0.4944	1:19.8
8th " " "	1.148	0.5760	1:25.5
9th " " "	0.515	0.3252	1:21.8

The average ratio is 1 : 21.5. The glycocoll production seems therefore a normal and constant factor of the proteid metabolism. Horse's urine taken at random showed ratios of 1:15 and 1:17 (see page 114).

The length of life under the condition of starvation generally depends upon the quantity of fat present in the organism at the start. The quantity of fat and proteid in an animal at the beginning of starvation or at any time during starvation may be estimated if the day-to-day metabolism be determined and if the whole animal be analyzed for fat and proteid at the time of death. The sum of the quantities remaining in the body, and the quantity of waste of previous days, will give the composition of the animal at any definite date during the experiment. E. Voit[1] shows that a rabbit with an original fat content of 7 per cent. lived nineteen days and lost 49 per cent. of his body proteid. Another rabbit with an original fat content of only 2.3 per cent. lived but nine days while the loss of body proteid amounted to 35 per cent. At the death of these rabbits the amount of fat found was very small, and the general vitality toward the end was almost exclusively maintained by the combustion of proteid. Other animals, however, which lost 22 to 26 per cent. of their proteid contained considerable fat at the time of death. E. Voit finds that the greater the amount of fat in the body, the less the proteid metabolism. In animals of equal fat content the relation between the amount of fat and the amount of proteid burned in the cells in starvation is always the same. When

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[1] E. Voit: "Zeitschrift für Biologie" 1901, Bd. xli, p. 545.

there is no fat, proteid may burn exclusively. From this it follows that *the quantity of the proteid metabolism in starvation depends upon the amount of fat in the body.*

E. Voit[1] has prepared the following table from an experiment of Schöndorff[2] upon a fasting dog. The quotient $\frac{\text{N content}}{\text{Fat content}}$ gives the ratio between these two components of the organism at the time specified. The ratio $\frac{\text{Energy N}}{\text{Energy total}}$ gives the percentage of the total energy derived from the proteid metabolism. The dog died on the thirty-eighth day of his fast.

PROTEID METABOLISM IN STARVATION AS INFLUENCED BY THE FAT CONTENT OF THE ANIMAL.

STARVATION DAY.	WEIGHT IN KG.	$\frac{\text{N CONTENT}}{\text{FAT CONTENT.}}$	EXCRETA N IN GRAMS.	ENERGY PER SQ. METER SURFACE.	$\frac{\text{ENERGY N}}{\text{ENERGY TOTAL.}}$ REDUCED TO %.
1st to 3d....	22.4	0.25	7.91	1040	26.5
4th to 13th...	20.7	0.29	5.38	974	16.2
14th to 15th..	19.7	0.34	5.70	959	18.1
16th to 23d...	18.7	0.40	5.71	944	19.1
24th to 30th..	17.4	0.57	5.92	919	21.3
31st to 35th..	16.2	0.87	6.62	901	25.6
36th.........	15.7	1.19	7.41	889	29.5
37th.........	15.5	1.34	8.41	887	33.8
38th.........	15.2	1.51	8.89	881	36.6

E. Voit finds that the amount of proteid metabolism depends so absolutely upon the relation between the amount of fat and proteid in the body (the $\frac{\text{N content}}{\text{Fat content}}$) that, knowing this ratio, he says he can estimate the relative proteid metabolism. When the ratio rises to 4.84 in the rabbit, then 98.3 per cent. of the total energy may be derived from proteid. Had fat still been present in any quantity the proteid metabolism would have remained low. This is the law which causes the gradual rise in the proteid metabolism during starvation, the "premortal rise," it has been termed. The increased combustion of the proteid is due to the requirement for energy in an organ-

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[1] E. Voit: *Loc. cit.*, p. 520.

[2] Schöndorff: "Pflüger's Archiv," 1897, Bd. lxvii, p. 430.

ism which has a constantly decreasing amount of fat upon which to draw.

The actual loss of body weight is greater when proteid is the source of energy than when the energy is derived from fat. The reason for this is that if one gram of nitrogen is lost there is a diminution of body weight of 33 grams, which represents just so much tissue waste and an energy yield of 0.8 calories per gram of "flesh" lost, while the combustion of one gram of fat simply causes the loss of one gram in body weight with an energy yield of 9.3 calories. To obtain equivalent amounts of energy there must therefore be a destruction of eleven and a half times more "flesh" by weight, than when fat is oxidized.

What is the cause of death from starvation? It does not seem to be due to an essential change in the composition of the cells themselves, for no chemical alteration has been detected in them.[1] What, then, is the cause of death? The general argument of E. Voit is as follows: It must be due either to a general failure of all the cells or injury of certain organs which are necessary for life. If the first cause were the true cause, then death would take place when a certain definite percentage of proteid loss occurred. This does not happen, since the body loss at the time of death may vary between 20 and 50 per cent. of its original content proteid. When the genital organs of the salmon develop at the expense of the liquefying muscle substance brought them by the blood, not a single muscle cell of the fish is killed, even though these lose 55 per cent. of their proteid in the process (Miescher). It seems extremely improbable, then, that a much smaller loss of proteid in starvation can be the cause of general cellular death. On the other hand, if death be due to the failure of certain organs, especially important to life, the cause is to be found in two factors. Either these organs receive too little nutrition for their proper functioning, or they become so emaciated that they fail in spite of sufficient

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[1] Abderhalden, Bergell, and Doerpinghaus: "Zeitschrift für physiologische Chemie," 1904, Bd. li, p. 153.

nutriment. Either the machine wears out or the fuel is insufficient for it.

The following table gives some answer to this. The general arrangement is in the order of the greater original fat content of the animals:

INFLUENCE OF FAT CONTENT ON PROTEID METABOLISM AND ON LENGTH OF LIFE IN STARVATION.

Animal.	First Weight, Kg.	Fat in %.		Loss in %.		Days before Death from Starvation.	Author.
		Start.	End.	Animal.	Body N.		
Dog	20.64	19	12	28	22	30	Falk.
Fowl	1.95	26	5	42	26	35	Schmanski.
Guinea-pig	0.67	16	10	38	26	10	Rubner.
Dog	23.05	11	1.7	34	35	38	Schöndorff.
Fowl	1.00	9.1	0.7	39	37	12	Kuckein.
Rabbit	1.51	7.1	0.4	49	49	19	Rubner.
Rabbit	2.53	6.3	0.5	44	49	19	Koll.
Rabbit	2.34	6.3	0.5	41	45	19	Rubner.
Fowl	1.89	2.7	0.7	34	41	9	Kuckein.
Rabbit	2.08	2.3	0.4	35	38	8	Kaufman.
Rabbit	2.99	2.3	0.3	32	35	9	Rubner.

In the first three animals a large amount of fat was present at the time of death, and this had prevented a great tissue waste. Abundant food was therefore available for the cells. The cause of death seems, therefore, to be in a reduction of activity in one or more organs important for life.

Again, if the proteid loss be kept down by administering proteid in quantity insufficient for the heating demands of the organism, the animal is kept living largely on his own fat. Schultz[1] in this way kept two dogs alive for twenty-eight and thirty-eight days, with losses of body nitrogen amounting to only 18 and 7 per cent. of the original quantity. The fat present was only 0.4 to 0.5 per cent. at the end. These dogs certainly suffered from no general loss of cell tissue. E. Voit concludes *that death from starvation is primarily due to loss of substance in organs important to life, but it may also ensue under certain circumstances as a result of deficient nutrition to these organs.*

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[1] Schultz: "Pflüger's Archiv," 1899, Bd. lxxvi, p. 379.

The question of what organs are attacked in starvation, has attracted attention. Long ago Voit[1] showed that the muscles of a cat which starved thirteen days lost 30 per cent., while heart, brain, and cord lost 3 per cent. only. In normally nourished animals E. Voit finds that the relative weights of the fat-free organs in animals of the same species are very constant. He[2] uses Kumagawa's[3] results to show what percentage the different organs represent in the fat-free organism of a dog before and after a twenty-four day fast. The third column represents the percentage loss of the fat-free organ in starvation:

LOSS IN WEIGHT OF DIFFERENT ORGANS DURING STARVATION.

Organ.	Fat-free Animal Contains in Percentage of Weight.		Fresh Fat-free Organ Loses in Percentage Weight during a 24 Days' Fast.
	Well Nourished.	Starvation.	
Skeleton	14.78	21.50	5
Skin	10.30	11.29	28
Muscles	53.77	48.39	42
Brain and Cord	0.94	1.11	22
Eyes	0.11	0.16	3
Heart	0.54	0.69	16
Blood	7.14	5.69	48
Spleen	0.39	0.26	57
Liver	3.98	3.05	50
Pancreas	0.33	0.19	62
Kidney	0.66	0.45	55
Genitals	0.30	0.23	49
Stomach and intestine	5.81	6.02	32
Lungs	0.89	0.97	29

It is apparent that the greatest loss is from the glands and the least from the skeleton. The activity of the glands is greatly reduced in starvation. Luciani found that there was no gastric juice formed during Succi's thirty-day fast, but Langley and Edkins find pepsinogen stored within the cells of the gastric glands. The bile flow continues up to the death of the person,

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[1] Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 355.

[2] E. Voit: *Ibid.*, 1904, Bd. xlvi, p. 195.

[3] Kumagawa: "Aus den Mittheil. d. med. Fakultät der kais. Japan. Univ.," Tokio, Bd. iii, No. 1.

but in diminished quantity, corresponding to the lack of food and the decreasing size of the liver. The writer[1] has noticed a great reduction in the activity of the milk secretion in starving goats, there being a permanent cessation of flow after five days. The percentage of fat increases in the milk, as it does in the blood, liver, and other organs.[2] The fasting organs attract fat from the fat deposits of the body and it is brought to them by the circulating blood. Dextrose is present in the blood up to the last day of life, having its probable origin in a constant production of sugar in proteid metabolism. The composition of the plasma of the blood in fasting as regards its proteid constituents varies very slightly from the normal. Lewinski[3] gives the following comparative analyses of blood-plasma of dogs:

100 C.C. BLOOD-PLASMA CONTAIN OF GRAMS N:

		Total.	Albumin.	Globulin.	Fibrinogen.
Dog I ...	Fasting	0.935	0.621	0.257	0.057
	Fed	0.831	0.511	0.240	0.080
Dog II...	Fasting	0.921	0.313	0.544	0.064
	Fed	1.062	0.515	0.423	0.124
Dog III..	Fasting	1.010	0.467	0.450	0.093
	Fed	0.977	0.475	0.402	0.100
	Fasting	1.096	0.554	0.443	0.099
Dog IV..	Fasting	1.052	0.536	0.324	0.192
	Fed	0.877	0.542	0.248	0.087

The only constant change seems to be a slight increase of globulin during fasting. Burckhardt believes this to be due to the passage of globulins from the tissues to the blood. Thus myosinogen, the principal proteid of muscle, may pass to the blood, possibly to become serum globulin and maintain the normal proteid content of the nourishing fluid of the body. The percentage of hemoglobin and the number of blood-corpuscles is not appreciably affected. It is evident then that the blood in

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[1] Lusk: Voit's Festschrift, "Zeitschrift für Biologie," 1901, Bd. xlii, p. 41.

[2] Rosenfeld: "Ergebnisse der Physiologie," 1903, Bd. ii, 1, p. 50.

[3] Lewinski: "Pflüger's Archiv," 1903, Bd. c, p. 631.

starvation retains the normal composition as regards its nutrient materials, except that it carries fat in increased quantity to the cells. In general the cells are well nourished for the ordinary maintenance of the life functions. Hence the appetite is not an expression of general cellular hunger, but rather the result of a local condition of the gastro-intestinal canal, which stimulates the individual to constant replenishment.

The glycogen of an animal is greatly reduced during starvation, but after twenty days it is not entirely removed.[1] Prausnitz[2] reports that a dog weighing 22 kilograms, after fasting for twelve days and after excreting 287 grams of sugar in the urine brought about by phlorhizin injections, still contained 25 grams of glycogen in his body. The writer[3] has found 0.4 gram of glycogen in the liver of a meat-fed phlorhizinized dog after eleven days of diabetes and an excretion of over 600 grams of sugar. Exercise will greatly reduce the glycogen content, but the only method of completely freeing the organism of glycogen is by tetanus.[4] Zuntz[5] rid a rabbit of glycogen by strychnin convulsions and then kept the rabbit fasting and under the influence of chloral for 119 hours. During this time 5.25 grams of sugar were excreted in the urine and yet 1.286 grams of glycogen were found in the liver and muscles. This must have gradually arisen from the proteid metabolism. The writer[6] made an observation that in a fasting diabetic rabbit tetanus produced an extra elimination of sugar in the urine of 1.1 grams, which undoubtedly was derived from the glycogen content of the organism. The quantity eliminated corresponded to the amount found as glycogen by Zuntz as above mentioned.

There now remains a discussion of the influence of work and of change in temperature upon the fasting organism.

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[1] Külz: Ludwig's Festschrift, 1891, p. 117.

[2] Prausnitz: "Zeitschrift für Biologie," 1892, Bd. xxix, p. 168.

[3] Reilly, Nolan and Lusk: "American Jour. of Physiol.," 1898, vol. i, p. 397.

[4] Külz: Ludwig's Festschrift, 1891, p. 119.

[5] Zuntz: Verhandl. der physiol. Ges. zu Berlin, "Arch. für Physiol." 1893, p. 378.

[6] Lusk: "Zeitschrift für Biologie," 1898, Bd. xxxvi, p. 111.

Frentzel[1] has shown the effect of external work upon the proteid metabolism of fasting dogs. One of the dogs did an amount of work corresponding to 216,937 kilogrammeters in three days. The proteid metabolism rose during the working hours and continued high on the fourth day which was one of complete rest (possibly the premortal rise had set in). Frentzel computes that the nitrogen elimination of these four days (= 20.7 grams) represents an energy equivalent of 220,300 kilogrammeters. This could not cover the work done by the dog if we add to the measured work that which was done by the heart and respiratory muscles. The proteid metabolism of four days is therefore entirely insufficient to cover the work done during three. The source of the energy for the work accomplished must therefore be found in an increased metabolism of fat. The increase in proteid metabolism above that of rest was not sufficient to supply 7 per cent. of the energy needed to do the work. The record of the dog's nitrogen metabolism is as follows:

INFLUENCE OF WORK ON THE N METABOLISM OF FASTING DOGS.

Day.	Work or Rest.	Food.	Grams of N Excreted.	
			Per Day.	Per Hour.
1st to 4th	Rest.	100 g. lard.	. . .	. . . . . .
5th	Rest.	100 g. “	3.13	0.1304
6th	Rest.	100 g. “	3.52	0.1467
7th	Rest.	Fasting.	3.71	0.1546
8th	Rest.	“	3.99	0.1663
9th	Work.	“	4.97	*0.3680 †0.1837
10th	Work.	“	5.02	*0.2750 †0.1960
11th	Work.	“	5.63	*0.2400 †0.2335
12th	Rest.	“	5.08	0.2117

*Work. † Rest.

Succi did not show a similar rise of proteid metabolism

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[1] Frentzel: "Pflüger's Archiv," 1897, Bd. lxviii, p. 212.

from the effect of work. The eleventh day of his fast he spent in bed. On the twelfth day he rode a horse for an hour and forty minutes, raced for eight minutes with some students, and gave an exhibition of fencing in the evening. During the day he walked 19,900 steps. The urinary nitrogen on the eleventh day (rest) was 7.88 g.; on the twelfth (work), 7.162; and on the days following 3.50, 5.33, 5.14, 5.05. The work done was evidently at the expense of increased metabolism of fat. That this is the case had already been demonstrated by Pettenkofer and Voit.[1] A fasting man at work showed no increase in his proteid metabolism, but the quantity of fat burned rose enormously. This is shown by the following comparison of the number of grams of fat burned:

	DAY.	NIGHT.
Rest	116 g.	94 g.
Work	312 g.	70 g.

The increase of fat metabolism during the day is two-and-a-half-fold and is presumably the source of the energy for the mechanical work accomplished. During the night following the working day the reduction of fat combustion as compared with the night before is due to more profound sleep.

Another phase of the effect of work is shown in the variation between the day and night metabolism of Tigerstedt's fasting medical student, J. A. The average carbon dioxid excretion in grams for two-hour periods during five days of fasting was as follows. The figures showing the elimination during the hours of sleep are printed in black letters.

	A. M.	P. M.					
Time	10–12	12–2	2–4	4–6	6–8	8–10	10–12
Carbon dioxid (grams)	54.8	57.2	54.1	57.8	59.5	66.4	**46.5**

	A. M.				
Time	12–2	2–4	4–6	6–8	...
Carbon dioxid (grams)	**37.5**	**39.1**	**40.7**	68.6	...

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[1] Pettenkofer and Voit: "Zeitschrift für Biologie," 1866, Bd. iii, p. 459; C. Voit: *Ibid.*, Bd. xiv, 1878, p. 144.

The nitrogen of the urine was also less during sleep than during the waking hours:

Fasting Day.	N in the Urine.	
	Day.	Night (10 P. M. to 10 A. M.)
1st	7.11	4.93
2d	6.87	5.85
3d	6.83	6.65
4th	7.91	5.65
5th	6.36	4.98

Johansson[1] finds that the inequality of night and day metabolism depends on muscular work. Sitting up raises the metabolism, and standing does so still more. Even when one lies in bed, restlessness during the day may increase the metabolism. And when perfect muscular relaxation ensues there may still be influences, such as light on the retina or sounds, which may act reflexly on the organism and slightly increase the metabolism. Johansson illustrates these variations in the following comparisons between night and day excretion of carbon dioxid of starving men, the night CO_2 being figured at 100.

	Night CO_2.	Day CO_2.	Author.
Complete muscular rest	100	105	Johansson.
Ordinary rest in bed	100	110	Johansson.
Ordinary life (no hard work)	100	142	Tigerstedt.
" " " " "	100	128	Pettenkofer and Voit.
" " " " "	100	147	Tigerstedt.

Johansson agrees with Tigerstedt that the minimum metabolism of a man in bed is represented by 24 to 25 calories per kilogram daily.

The temperature of the fasting organism is usually normal. Luciani found a normal temperature in Succi during his thirty-day fast. The temperature falls only a few days before death. Sonden and Tigerstedt[2] find that the diurnal variations per-

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[1] Johansson: "Skandinav. Archiv für Physiologie," 1898, Bd. viii, p. 109.

[2] Sonden and Tigerstedt: *Ibid.*, 1895, Bd. vi, p. 136.

sist during fasting in their ordinary rhythm. The average temperature of the medical student J. A. during his five-day fast was but 0.16° below his normal temperature when food was allowed him. These diurnal vaiations are exactly concomitant

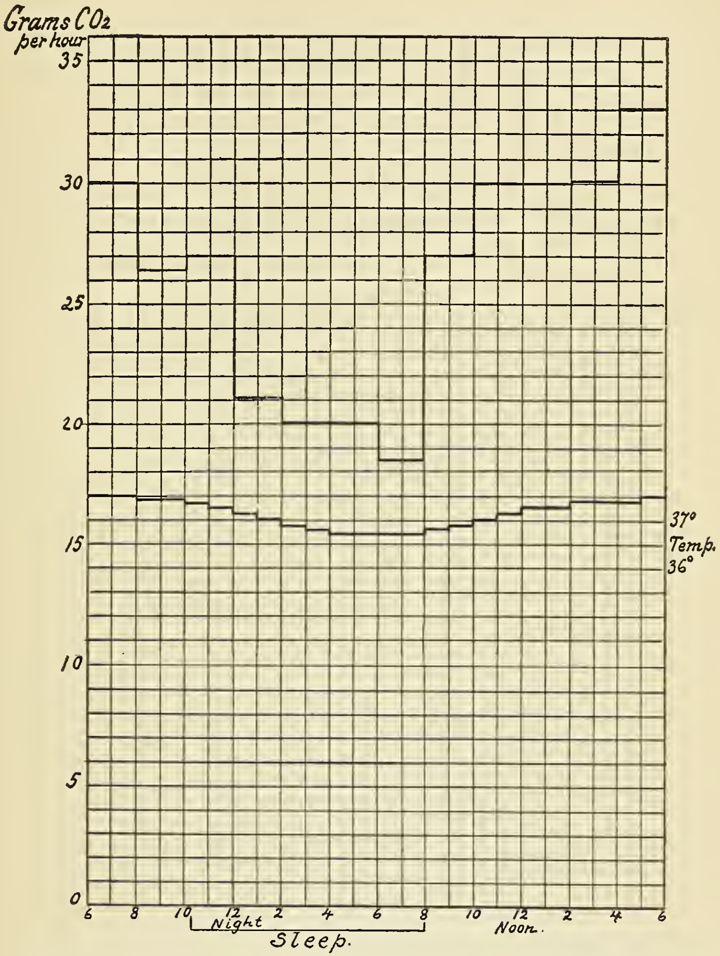

Fig. 1.—Curve of carbon dioxid elimination compared with Jürgensen's curve of normal diurnal temperature variation. This individual led a normal life and partook of his usual nourishment.

with the fluctuations of carbon dioxid excretion noted on a previous page. When the carbon dioxid production increases, the temperature rises.

This parallelism may be easily shown by comparing the two factors in the preceding chart as given by Sonden and Tigerstedt.[1] Furthermore, the diurnal variations tend to disappear if the person be kept in a state of muscular rest, and the day and night metabolisms remain the same. In this state the temperature may fall 0.6° below the normal on account of the absence of muscle movement. This regularity of temperature and metabolism is beautifully shown in the following chart of Johansson:[2]

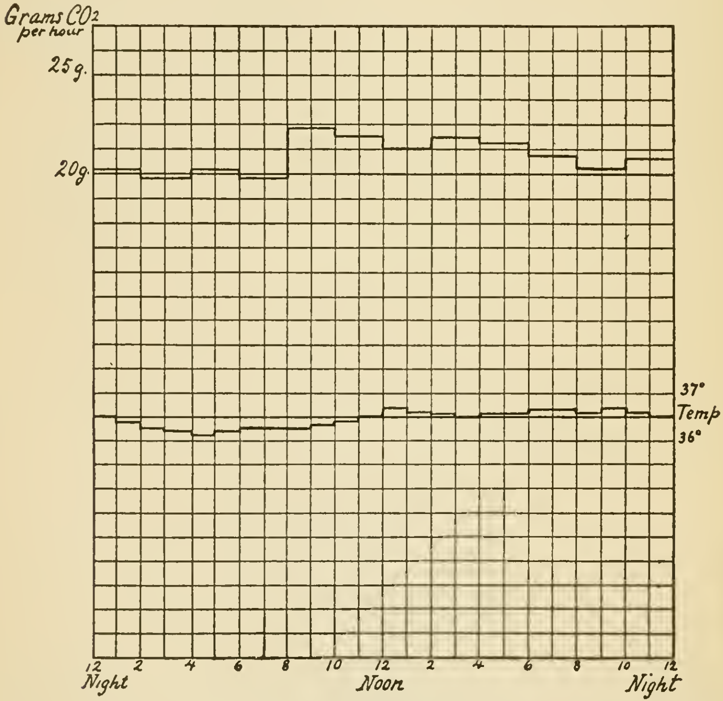

Fig. 2.—Carbon dioxid elimination and body temperature in fasting and complete muscular rest.

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[1] Sonden and Tigerstedt: *Loc cit.*, p. 132.

[2] Johansson: *Loc. cit.*, p. 142.

Inversion of the normal routine of life, so that one sleeps in the daytime and is awake and active at night, brings about an inversion of curve of body temperature. This is well shown in the monkey.[1]

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[1] Goldbraith and Simpson: Proceedings of the Physiological Society, "Journal of Physiology," 1903, vol. xxxiii, p. xx.

CHAPTER IV.

THE REGULATION OF TEMPERATURE.

It has been seen that the temperature of a warm-blooded animal is maintained at the normal throughout a fast. Not only this, but it is maintained at the same level, even though the temperature of the outside environment vary from 0° and lower to 30° to 35°. In cold-blooded animals the temperature of the body is only slightly higher than that of their environment at the time. The metabolism of such animals varies with the temperature. The frog in the mud during the winter at a temperature of 4° C. has quite a different metabolism from that which he enjoys during the summer sunshine as he sits on the river-bank or snaps at passing flies. The curve of his carbon dioxid elimination at various temperatures has been made by E. Voit from the analyses of H. Schultze, and is given below:

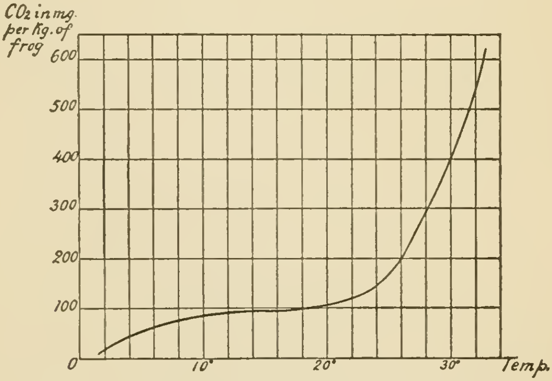

Fig. 3.—CO_2 in milligrams per hour per kg. frog.

A sudden rise in the frog's metabolism commences at about 20°. A temperature of 20° corresponds to that of the bear and marmot during their winter's hibernation, and is a level of comparatively low metabolism. This reduction in activity is exemplified by the fact that a cat whose temperature has been artificially reduced to 19° may have but one heart-beat per minute.[1]

E. Voit[2] has drawn attention to the fact that the above curve of increasing metabolism with increasing temperature corresponds to the increasing ability of the frog's muscle to contract, and to the increasing effectiveness of enzymotic activity. A warm temperature is necessary for the irritability and activity of protoplasm. The warmth of the sunshine increases the irritability of the protoplasm of the tree in the spring, with the resulting development of the foliage. Heat is not the cause of the metabolism, but only one of the conditions for it. In warm-blooded animals the temperature is maintained at a constant level independent of climatic conditions, and this level is a favorable one for the activity of nerve and muscle. It would indeed be inconvenient were the active life of a man dependent upon the temperature of his environment. The essential mechanism for the regulation of the body temperature is through the nerves. The action of cold on the skin may stimulate its peripheral nerve-endings which are sensitive to cold, and reflexly effect in the organism a greater heat production, and a vaso-constriction of peripheral blood-vessels: the action of heat, on the contrary, effects vasodilatation and production of sweat. It is believed that the cold-blooded progenitors of warm-blooded animals changed their habitat from the sea to the land at a tropical temperature which is at present possessed by their descendants. In the course of development these animals acquired the power to maintain that ancestral temperature, which proved favorable for the activity of their body substance. The nervous mechanism through which this is accomplished is twofold: First, there is an increased production of heat in the presence of external

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[1] Simpson and Herring: "Journal of Physiology," 1905, vol. xxxii, p. 305.

[2] E. Voit: "Sitzungsber. der Ges. für Morph. und Physiol.," 1896, Heft III.

cold (*the chemical regulation of temperature*), and, second, there is a variation of the distribution of blood on the surface of the body in order to modify heat loss and there may be an increased evaporation of water from the body (production of sweat) to serve the same purpose (these are the factors of the *physical regulation of temperature*). The great importance of these two controlling influences will be seen as the subject develops.

If the body were a mass of cells having the shape of a ball with a constant heat production in its center, it would be easy to calculate its temperature in the different zones of the interior. The loss of heat from the surface would obviously be equal to the heat production, if the temperature of the ball continued constant.

If two balls of the same material, but of unequal size, were equally warmed, the smaller would cool more quickly than the larger on account of the relatively greater exposed surface from which heat could be discharged. The heat elimination would be proportional to the surface exposed.

To determine the surface of geometrically similar solids, and hence of animals of similar shapes, the following formula was used by Meeh[1] in which S = surface and V = volume:

$$\frac{S}{V^{\frac{2}{3}}} = \frac{S\sqrt[3]{V}}{V}$$

Since animals contain the same materials, one may substitute W = weight for V.

Then the value $\frac{S\sqrt[3]{W}}{W}$ may be empirically determined for each shape or animal, and this value = k. Hence the formula would read:

$$\frac{S}{W^{\frac{2}{3}}} = k \text{ or } S = k\sqrt[3]{W^2}$$

The value of *k* or the constant in the relationship of weight to surface in each animal has been given by Rubner as follows:

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[1] Meeh: "Zeitschrift für Biologie," 1879, Bd. xv, p. 425.

Man	12.3
Dog	11.2–10.3
Rabbit	12.9–12.0
Rabbit (without ears)	10.8
Calf	10.5
Sheep	12.1
Cat	9.9
Pig	8.7
Guinea-pig	8.5
Fowl	10.4
Rat	9.1
White mouse	11.4

The use of the above formula rendered possible the calculation of the heat elimination per unit of area in fasting animals during rest. When these have been previously well fed, there is a surprising uniformity of result. It is Rubner's law that the metabolism is proportional to the superficial area of an animal. In other words, the metabolism depends on the amount of heat loss at the surface, and its variation in accordance with this law is necessary for the maintenance of a constant temperature.

Erwin Voit[1] has calculated the following general table showing the heat production in resting animals of various sizes at medium temperatures of the environment:

		Calories Produced.	
	Weight in Kg.	Per Kilo.	Per Sq. M. Surface.
Horse	441	11.3	948
Pig	128	19.1	1078
Man	64.3	32.1	1042
Dog	15.2	51.5	1039
Rabbit	2.3	75.1	776
Goose	3.5	66.7	969
Fowl	2.0	71.0	943
Mouse[2]	0.018	212.0	1188
Rabbit[2] (without ears)	2.3	75.1	917

The universality of this law of Rubner's is remarkable. Even at a room temperature of 30° where all thermal influence is removed, two guinea-pigs of different sizes will produce heat in proportion to their surface. In this case there is a minimum of heat production determined for the resting organism according to the law of superficial area.

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[1] E. Voit: "Zeitschrift für Biologie," 1901, Bd. xli, p. 120.

[2] Rubner: "Energiegesetze," 1902, p. 282.

When this discovery was first made, the interpretation was offered that the metabolism in the different animals was in proportion to the skin area, because of the specific sensory influences of cold proceeding from a definite surface (chemical regulation). This explanation fell when Rubner discovered that at a temperature of 30°, under which condition all thermal stimulus to the organism ceased, two guinea-pigs of different sizes still produced heat in proportion to their skin areas. A similar fact was noted by Frank and Voit[1] who found that the administration of curare, which paralyzes the voluntary muscles, scarcely affected the carbon dioxid output of a dog as compared with what was eliminated during ordinary muscular rest, provided the temperature of the animal was maintained at the normal by keeping him in a warmed chamber. The mass of living cells preserved the same metabolism as before, even though a pathway of heat increase had been cut off through paralysis by curare of the motor nerve-endings in the muscles. Keeping the animal in a warmed chamber was necessary in this case, for Röhrig and Zuntz[2] had shown that curarized animals at the ordinary room temperature lost the power of maintaining their body temperature and that their metabolism decreased accordingly. The removal of the chemical regulation caused a behavior toward external temperature similar to that in cold-blooded animals.

Although the effect of cold on the skin (inducing chemical regulation) was of itself demonstrably insufficient to account for the "law of skin area," Rubner[3] argues that even at 30° C., when the body is losing heat by means of the dilatation of the blood-vessels and the evaporation of water (physical regulation), the law is still a necessity if the general mechanism for loss of heat in the various animals is the same in all. An infant produces 90 calories per kilogram in twenty-four hours, an adult 32 calories. Were the metabolism of an adult 90 calories per

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[1] Frank and Voit: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 309.

[2] Röhrig and Zuntz: "Pflüger's Archiv," 1871, Bd. iv, p. 57.

[3] Rubner: "Energiegesetze," 1902, p. 174.

kilogram, the means of heat elimination through his comparatively smaller surface would have to be materially modified if a normal temperature were to be maintained with comfort.

The organism therefore preserves the tropical temperature of its cells at the expense of a metabolism which is proportional to the skin area of the individual.

The loss of heat by an organism is by the following paths:

1. Conduction and radiation.
2. Evaporation of water from lungs and skin.
3. Warming the food ingested.
4. Warming the inspired air (conduction).

The great outlets for heat loss are by conduction and radiation (of which in the dog 97.3 per cent. takes place through the skin and 2.7 per cent. through the lungs[1]) and through the evaporation of water. The losses through warming the food, and through heat of solution of urinary constituents, through the feces and the warming of expired carbon dioxid may be ordinarily disregarded.

The pathway for the loss of heat varies with the temperature of the environment. At a low temperature there is little evaporation of water, and at a temperature of 37° there can be no heat loss by radiation and conduction (except by a rise in body temperature) and water evaporation removes the whole of it. In the dog at a high temperature there is distention of the limbs to promote heat loss by radiation and conduction, and rapid breathing (polypnea) with extension of the hyperemic tongue to promote evaporation of water. In the horse and in man there is especially an outbreak of sweat, which is not possible in the dog as its skin does not secrete sweat.

It has been seen that Lavoisier noticed that cold increased the metabolism. This has been abundantly confirmed. The simplest illustration of this action is to be found in fasting animals. Rubner has called this increase of combustion, and therefore of heat production, the *chemical regulation* of the body temperature. It is the same as burning more coal in the fur-

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[1] Rubner: "Energiegesetze," 1902, p. 187.

nace on a cold day in order to maintain the temperature of the house. Voit had previously demonstrated this action in the case of a man (see below).

Rubner placed a fasting guinea-pig in a bell-jar which was ventilated so that the carbon dioxid production could be determined. The temperature of the bell-jar could be changed by immersing it in water. The following were the results:

ACTION OF CHEMICAL REGULATION IN THE GUINEA-PIG.

Temp. of Air.	Temp. of Animal.	Grams of CO_2 in 1 Hr. per Kg. Animal.	Percentage Change of CO_2 for Each 1° C. Rise in Temp. of Air.
0.0°	37.0	2.905	—2.33
11.1°	37.2	2.151	
20.8°	37.4	1.766	—1.84
25.7°	37.0	1.540	—2.67
30.3°	37.7	1.317	
34.9°	38.2	1.273	—0.71
40.0°	39.5	1.454	+2.82

It is evident from the table that there was a constant decrease in the metabolism as the air was warmed from 0° to 35° C. The metabolism at 0° was two and a half times that at 30°, an increase as pronounced as is incurred as the result of severe muscular work. The animal at 0° was not observed to move around any more than he did at 30°. Other experiments confirmed Rubner in the view that the *critical temperature*, or the temperature of the minimum metabolism, lay at 33°. At this point temperature had the least influence on total metabolism. When the temperature is raised from 30° there is at first no increase in the metabolism. This is due to the action of the apparatus for the *physical regulation* of body temperature. Accompanying a rising temperature the blood-vessels of the skin become dilated and the evaporation of water from the body is promoted. These factors tend to maintain the normal temperature of the organism by physical means. If the temperature of the air be high, so that the physical regulation be not sufficient to cool the body, then a hypernormal temperature ensues. Such a febrile temperature raises the metabolism by warming the cells, as was seen in the table of the experiment in which the guinea-pig was exposed to a temperature of 40°. The range of the physical regulation—that is, the period during which external temperature change does not alter metabolism—depends, according to Rubner, on the natural protections which an animal possesses which insure him against heat loss. These are two in number—the hairy covering, and the thickness of the layer of subcutaneous fat.

Rubner has shown that the hair of the black cat, black lamb, rabbit, skunk, raccoon, mink, musk-deer, and sheep is of itself relatively light in weight, but that the fur contains a very large quantity of air. The whole of the fur covering of these animals consists of between 97.3 and 98.8 per cent. of air. The fur therefore really consists of air with between 1.2 and 2.7 per cent. of hair. The slight conductivity of the fur is principally dependent on this layer of stationary air. If an animal be covered with a fur containing this stagnant air, he will be better protected from loss of heat than if he had none, and also less susceptible to the influence of cold upon the surface of his skin. This protective covering therefore extends the range of the physical regulation.

Rubner[1] gives the following experiment showing the influence of temperature on a small fasting dog with long hair:

ACTION OF CHEMICAL REGULATION IN THE DOG.

Day.	N in Urine.	N in Feces.	Total N.	C of Respiration.	C of Urine.	Total C.	C from Fat.	Cal. from Proteid.	Cal. from Fat.	Total Calories.	Temperature.
1st	1.80	0.06	1.86	20.0	1.1	21.0	14.9	46.5	183.6	230.1	20.0°
2d	1.56	0.06	1.62	22.4	1.0	23.4	18.0	40.4	224.6	264.6	15.2°
3d	1.52	0.06	1.58	28.2	1.0	29.1	23.9	39.5	294.7	334.2	7.6°
4th	1.56	0.06	1.62	18.9	1.0	19.9	14.5	40.5	179.0	219.5	30.0°
5th	1.42	0.06	1.48	17.3	0.9	18.2	13.7	37.0	169.3	206.3	25.2°

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[1] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 105.

One observation was made in this experiment on the dog which was not possible in the case of the guinea-pig, and that concerned the nitrogen excretion. The nitrogen excretion for twenty-four hours is not increased by exposing the dog to a temperature of 7.6°. The increased metabolism is entirely at the expense of fat. We have seen that this may also be true of work which may be accomplished at the expense of fat without raising the proteid metabolism.

Reduced to terms of calories produced per kilogram of dog, the following results are obtained:

Temperature.	Calories per Kilo.
7.6°	86.4
15.0°	63.0
20.0°	55.9
25.0°	54.2
30.0°	56.2
35.0°	68.5

A temperature of 20° was readily borne by this dog without any increase of his metabolism. The period of no chemical change extended over at least ten degrees between 20° and 30°, during which time the physical regulation alone sufficed to maintain evenly the body's temperature. At 35° a decided increase of heat production set in, on account of the warming of the cells through insufficient heat loss. That the range of the physical regulation of the temperature of this small dog was due to his long hair is shown by the change in his metabolism after shaving him. Rubner shows this in the following table:

Temperature.	Calories per Kilo.	
	Normal Coat of Hair.	Shaved.
20°	55.9	82.3
25°	54.2	61.2
30°	56.2	52.0

It is clearly seen that this dog lost his power of physical regulation between 20° and 30° as soon as he lost his covering of hair. His metabolism became like that of the guinea-pig, increasing with a reduction of temperature from 30° downward, an illustration of chemical regulation.

E. Voit[1] shows that the metabolism of a pigeon may be doubled after removing his feathers.

Babak[2] finds that if rabbits are shaved and varnished with starch paste their metabolism rises 140 per cent., which increase maintains their body temperature at the normal for several weeks, although the room temperature be between 15° and 20°.

To determine the influence of the second factor, that of the protecting layer of fat, Rubner[3] investigated the influence of temperature on the metabolism of a fasting short-haired dog, at a time when he was emaciated, and compared it with the fasting metabolism after the same dog had been fattened. The results were as follows:

Dog (Thin).		Same Dog (Fat).	
Temperature.	Cal. per Kilo.	Temperature.	Cal. per Kilo.
5.1°	121.3	7.3°	120.5
14.4°	100.9	15.5°	83.0
23.3°	70.7	22.0°	67.0
30.6°	62.0	31.0°	64.5

It appears from the above that the metabolism of the dog was the same at a low temperature in both cases, but that the minimum metabolism was almost reached at a temperature of 22° in the dog when he had a protective covering of fat, which was not the case when he was thin. The presence of adipose tissue, therefore, acts in the same way as does a warm fur to extend the range of the physical regulation, and to delay the onset of the chemical regulation of body temperature.

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[1] Voit: "Sitzungsber. der Ges. für Morph. u. Physiol.," 1904. Bd. xix, p. 39.

[2] Babak: "Pflüger's Archiv," 1905, Bd. cviii, p. 389.

[3] Rubner: *Ibid.*, 1902, p. 137.

The physical regulation may be increased by certain voluntary acts, such as are observed when a dog exposed to cold lies down and curls himself up in such a way as to offer as small an exposed surface as possible. The contrast to this is offered when on a hot day the dog lies on his back and extends his limbs so as to promote the loss of heat.

Rubner[1] compared the fasting metabolism of a resting dog exposed to air at about 18° with that of the same dog quietly resting suspended in a net, by which means his surface was more exposed to the influence of cold. The results were as follows:

	Day of Starvation.	Cal. from Proteid.	Cal. from Fat.	Total.	Temp.
Resting	2	33.79	430.91	464.7	17.5°
Resting in net	3	33.79	581.50	615.2	18.2°

Rubner[2] also cites an important modification of metabolism through a variation in the humidity of the atmosphere.

At a medium temperature during fasting (as well as on a medium diet) the metabolism of a dog was practically unaffected by an increase of humidity in the air, as appears below:

Temperature 20.2°	Cal. in 24 Hours.	Humidity in Per Cent.
Dry day	258.4	34
Humid day	256.6	69
More on dry day	1.8	

However, on a liberal diet the metabolism increases on a damp day even at a medium temperature, as for example:

Temperature 20.2°	Cal. in 24 Hours.	Humidity in Per Cent.
Very dry day	249.4	13
Humid day	261.9	66
More on humid day	12.5	

The increase is 5 per cent.

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[1] Rubner: "Energiegesetze," 1902, p. 184.

[2] Rubner: *Ibid.*, 1902, p. 188.

On a very hot day (on a moderate fat diet) the dog's metabolism is increased by the presence of moisture in the atmosphere.

TEMPERATURE 35°.

Calories per Kg.	Humidity in Per Cent.
69.28	9.1
73.54	30.0

Under these circumstances the metabolism rose 6.1 per cent. in the more humid air. There was probably an overwarming of the cells, on account of the difficulty of heat loss by evaporation of water. A cold damp climate of 0° to 5° temperature also favors an increased metabolism. Rubner attributes this action of humidity to the increased conductivity of a hair covering containing moisture, and says that this loss may be partially balanced by a decreased evaporation of water from the lungs.

The metabolism and the manner of heat loss may therefore be variously affected by the condition of the atmosphere as regards moisture.

On days of ordinary dryness Rubner[1] calculates the following division of the heat loss in a starving dog under the influence of different temperatures:

INFLUENCE OF TEMPERATURE ON MANNER OF HEAT LOSS.

TEMPERATURE.	CALORIES LOST BY CONDUCTION AND RADIATION.	CALORIES LOST BY EVAPORATION OF WATER.	TOTAL CALORIES OF METABOLISM.	HUMIDITY IN PER CENT.
7°	78.5	7.9	86.4	24
15°	55.3	7.7	63.0	34
20°	45.3	10.6	55.9	29
25°	41.	13.2	54.2	19
30°	33.2	23.0	56.2	14

It is clear that at 7° only a little heat is lost by the evaporation of water and the greater part by conduction and radiation. As the surrounding air becomes warmer the power to lose heat by radiation and conduction diminishes and the loss through the evaporation of water increases.

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[1] Rubner: "Energiegesetze," 1902, p. 189.

Rubner has charted this experiment after making allowances[1] for the varying moisture conditions. The chart is here reproduced:

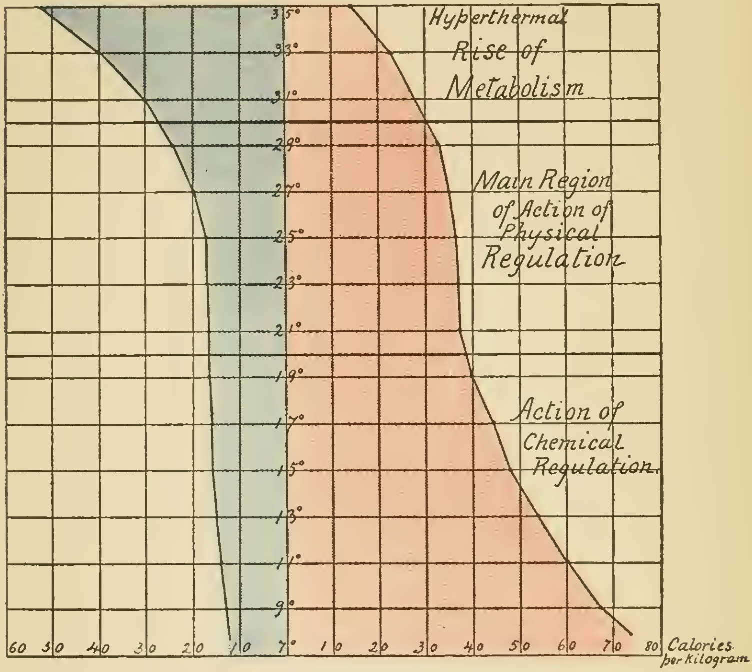

Fig. 4.—Rubner's chart showing the manner of heat loss at different room temperatures in the dog. *Blue,* Heat loss in calories through evaporation of water. *Red,* Heat loss in calories through radiation and conduction.

The distance between opposite points of the curved line represents the total metabolism at a particular temperature.

The chart epitomizes the method of heat loss in a starving dog under the influence of varying temperatures.

The discussion of the metabolism has given a foundation for the understanding of the basic requirement of an organism. The minimum requirement for energy is seen to be present when the fasting organism is surrounded by an atmosphere having a temperature of 30° to 35°. This may be called the

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[1] Rubner: "Archiv für Hygiene," 1891, Bd. xi, p. 208.

basal requirement, the minimum of energy compatible with cell life. This basal requirement is modified by temperature, by food, and by work, and it is an important factor to keep in mind (see p. 177).

The principles laid down here regarding the lower animals apply equally to man. He too may come under the influence of chemical regulation, although he constantly endeavors to maintain the surface of his skin at a tropical temperature through the use of clothes. His heat loss may, like the dog's, be more difficult if he be covered with a thick layer of fat. And his metabolism is also influenced by atmospheric conditions of moisture, wind, and temperature.

One of the earliest demonstrations of the action of chemical regulation was afforded by Voit, who placed a fasting man weighing 70 kilograms in the Pettenkofer-Voit respiration apparatus and determined the carbon dioxid and nitrogen output for six hours. The person accustomed himself to the given temperature by staying under its influence for some time previous to the commencement of the experiment. In the cold experiments the ventilating air was derived from the winter atmosphere. On the very warm days the air was artificially heated. Voit[1] gives the following results:

EFFECT OF TEMPERATURE ON THE METABOLISM OF A FASTING MAN.

Temperature.	CO_2 Excreted in G.	N in Urine in G.
4.4°	210.7	4.23
6.5°	206.0	4.05
9.0°	192.0	4.20
14.3°	155.1	3.81
16.2°	158.3	4.00
23.7°	164.8	3.40
24.2°	166.5	3.34
26.7°	160.0	3.97
30.0°	170.6	...

The nitrogen elimination remains unaffected by temperature. At the ordinary room temperature there scarcely seems to be any increase in carbon dioxid output, but at the lower temperatures the quantity of the fat metabolism is markedly increased,

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[1] Voit: "Zeitschrift für Biologie," 1878, Bd. xiv, p. 80 .

as shown by the rise of carbon dioxid elimination. The individual sat quietly in a chair, but at a temperature of 4.4° could not prevent himself from shivering.

The whole effect of the chemical regulation in man has been attributed by Johansson[1] to the additional metabolism due to shivering. Voit did not believe that this could be the cause, nor that the increased respiratory activity could account for the rise in metabolism. Voit believed the increase to be a reflex stimulus of cold on the skin which raised the power of the muscle cells to metabolize. Voit's views have been confirmed in Rubner's laboratory[2] in the following series of experiments on a man:

TEMPERATURE.	CO_2 IN GRAMS PER HOUR.
15°	32.3
20°	30.0
23°	27.9
25°	31.7
29°	32.4

In this experiment there was no shivering at a temperature of 15° and yet the metabolism increased from what it was at 23°.

It has also been shown that cool baths and winds increase the metabolism, which must be effected through the chemical regulation. Lefévre[3] states that a man, who has been inured to it, may sit naked for several hours in a cold wind without loss of body temperature.

Rubner[4] has measured the effect of baths and douches lasting three and a half to five minutes. When the water has a temperature of 16° he finds that the carbon dioxid elimination may be very largely increased, especially in the case of the douche. The effect of the douche was more marked if taken before breakfast when the intestinal tract is free from food. The results before breakfast were as follows:

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[1] Johansson: "Skan. Archiv. für Physiologie," 1896, Bd. vii, p. 123.

[2] Rubner: "Energiegesetze," 1902, p. 203.

[3] Lefévre: "Comptes rendus," 1894, p. 604.

[4] Rubner: "Archiv für Hygiene," 1903, Bd. xlvi, p. 390.

INFLUENCE OF COLD BATHS ON METABOLISM IN MAN.

	Douche 16°. Increase in per Cent.	Bath 16°. Increase in per Cent.
Volume of respiration	54.5	22.9
Carbon dioxid excreted	149.5	64.8
Oxygen absorbed	110.1	46.8

A cold bath, especially a douche, will therefore stimulate to a greatly increased metabolism. The respiratory quotient indicates that the increased metabolism is at the expense of the glycogen supply. There is an after-effect which lasts about one and a half hours, indicating an increased metabolism during that time. This may be the expression of the body's attempt to maintain a normal temperature after being somewhat cooled (see also p. 254).

It is obvious that a cold bath will be liable to induce shivering unless by mechanical effort, such as swimming, the metabolism is increased so as to supply calorific energy in another way than through chemical regulation.

A bath of 35° has no effect on metabolism.

Rubner finds that a bath at 44° again increases the metabolism, the increase being, for the volume of respiration, 18.8 per cent., for carbon dioxid 32.1 per cent., and for oxygen 17.3 per cent. This is probably due to the overwarming of the cells. Baths at this temperature find favor among the Japanese.

The effect of wind is such that an imperceptible air current may have a very pronounced effect. Rubner[1] has shown that wind becomes perceptible when it attains a velocity of 0.4 to 0.5 meter a second, and that if a wind much below this *threshold* value, having a velocity of 0.18 meter per second, act upon the exposed area of the arm, there is an increased heat loss of between 19 and 75 per cent., depending on the temperature of the wind, above what would be lost were the air quiet.

The effect of wind of moderate humidity and different temperatures on the metabolism of a man clad in summer clothes, as compared with the metabolism during atmospheric calm, is shown in Wolpert's[2] experiment below:

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[1] Rubner: "Archiv für Hygiene," 1904, Bd. l, p. 296.

[2] Wolpert: *Ibid.*, 1898, Bd. xxxiii, p. 206.

INFLUENCE OF WIND ON METABOLISM IN MAN.

Temperature.	Calm. Grams CO_2 per Hour.	Wind 1 Meter per Second. Grams CO_2 per Hour.	Wind 8 Meters per Second. Grams CO_2 per Hour.
2°	29.8	....	....
10–15°	25.1	28.3	30.0
15–20°	24.1	....	30.1
20–25°	25.0	....	28.0
25–30°	25.3	22.2	24.4
30–35°	23.7	....	21.6
35–40°	21.2	22.2	22.1

According to this a breeze having a temperature of 15–20° and moving at the rate of about 15 miles per hour (8 meters per second) has a greater effect upon the metabolism of a man clad in summer clothing than a temperature of 2° would have during perfect atmospheric quiet. In all the experiments the smallest amount of carbon dioxid is eliminated between 30° and 40°.

The above experiments were performed on a thin man, and it will be noticed that there was no rise in his metabolism at a temperature of between 35° and 40°. Rubner explains this as due to the sufficiency of the evaporation of perspiration on the surface for the cooling of the organism.

A fat man, however, with a thick, ill-conducting layer of adipose tissue, is not so immune to the effect of high temperatures upon his metabolism. This is especially pronounced in a damp climate. Thus Rubner[1] obtains the following results from a fat man wearing clothes:

INFLUENCE OF TEMPERATURE AND HUMIDITY ON THE METABOLISM OF A FAT MAN.

Temperature.	Humidity 30 per cent.		Humidity 60 per cent.	
	CO_2 in grams per hour.	H_2O evaporated per hour.	CO_2 in grams per hour.	H_2O evaporated per hour.
20°	33.7	56	30.7	17
28–30°	36.9[1]	134	44.5[3]	170+ 31 g. sweat.
36–37°	42.6[2]	204 +14 g. sweat.	46.7[4]	186 +255 g. sweat.

[1] Body temperature rose 0.1°
[2] " " " 0.0°
[3] Body temperature rose 0.4°
[4] " " " 0.9°

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[1] Rubner: "Energiegesetze," 1902, pp. 208, 232.

The fact that in the experiment where there was 30 per cent. humidity the metabolism largely increased at 36–37° without concomitant rise in body temperature, leads Rubner to theorize that there must have been an overheating of the cells where the metabolism was progressing, even though this might not have been determinable by the clinical thermometer.

It appears that on a hot, humid day the metabolism of a fat individual may be fifty per cent. higher than on a day of moderate temperature and the same humidity. The whole of the body heat is lost through the evaporation of water which is here hindered by the humidity; and besides, there is a large excretion of sweat which is always accompanied by a feeling of physical exhaustion. At a moderate temperature, where the greater part of the heat loss is by radiation and conduction, the excretion of water is not excessive.

There can be no doubt that climatic conditions modify racial characteristics. The emigrant from Northern Europe, living upon a farm in the hot and often moist climate of an American summer, must restrict his layer of adipose tissue if he is to live comfortably. The same holds true in Italy. The difference between John Bull and Uncle Sam seems to be one of climatic adaptation On the contrary, the Eskimo cultivates a thick, fat layer to protect himself from frost. It is also interesting to note that prostrations from the heat appear in New York with 66 per cent. humidity and a temperature of 31.5° (2.30 P.M., August 24, 1905). Rubner[1] says that a lightly clad thin man, at a temperature of 30° with humidity at 65 per cent., bore the effect so badly that he feared to raise the temperature to 35°. This individual had readily tolerated 35° in dry air.

The maximum mortality from "summer troubles" in children in New York coincides with the first great wave of heat accompanied by humidity which falls upon the city. Similar climatic conditions at later dates are not so fatal. It may be that the fatality of these intestinal affections is due to the inefficiency of the apparatus for the physical discharge of heat in

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[1] Rubner: "Energiegesetze," 1902, p. 232.

the infant organism. It is also possible that infection may be more readily achieved under these conditions (p. 183).

Another factor in the heat regulation of man is clothes. Certain savage races do without clothes, as, for example, natives of Terra del Fuego, who substitute a covering of oil. In such races the process of "hardening" or the development of the physical regulation must be carried to a maximum. In civilized countries man endeavors to remove all the influence of chemical regulation by keeping his skin covered. Only about 20 per cent. of his surface is normally exposed to the air. The most important constituent of clothes is the air, which is a much worse conductor of heat than is the fiber. This is especially true of furs (p. 85). Thickness of the cloth will give a greater layer of air and will prevent heat loss from the body. A densely woven cloth prevents proper ventilation and does not absorb moisture. In hot weather a porous cloth next to the skin which can absorb moisture and permit its ready evaporation is of high importance. If such a garment become thoroughly wet the evaporation of sweat at a high temperature is largely prevented, to the great discomfort of the individual, while at a lower temperature heat loss through conduction is greatly facilitated, with a sensation of chill. Two experiments cited by Rubner[1] indicate the effect of clothes on metabolism. An individual was kept at a temperature of between 11 and 12° and wore different clothes at different times. His carbon dioxid and water excretion were as follows:

INFLUENCE OF CLOTHES ON METABOLISM IN MAN AT A TEMPERATURE OF 11–12°.

	CO_2 in Grams per Hour.	H_2O in Grams per Hour.	Remarks.
Summer clothes	28.4	58	Cold, occasional shivering.
Summer clothes and winter overcoat	26.9	50	Chilly part of the time.
Summer clothes and fur coat	23.6	63	Comfortably warm.

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[1] Rubner: "Energiegesetze," 1902, p. 225.

When the man was comfortable the chemical regulation of temperature was eliminated.

Rubner points out that while the radiant energy of the sun is large in quantity, he has been unable to find any influence upon a man under ordinary circumstances, but believes that it may take the place of heat produced through chemical regulation on cold days. Thus a person living in the high altitude of Davos, Switzerland, feels much more comfortable in the sun on a cold day than he does in the shade. However, Zuntz while living on the summit of Monte Rosa found that sunlight did not reduce metabolism (p. 218).

In what follows it will be shown that the ingestion of food may add to the heat production of the organism and diminish the necessity of heat production through chemical regulation in cold weather. Also, it may very uncomfortably increase the production of heat and perspiration in warm weather, especially if proteid be largely taken (p. 183).

From this chapter the influence of climate is seen to be noteworthy. It explains why a temperature of —40° may be comfortably borne in winter, in the Adirondacks, for example, if the air be dry and still; how a much warmer atmosphere which is damp and windy may "cut to the bone" with cold; how a hot, dry climate may be entirely comfortable, when air at the same temperature laden with moisture may strike down many fatally and oppress every one; and how the effect of heat may be modified by the breezes and baths at the seashore.

It does not explain the effect of the dry sirocco wind which blows from the Desert of Sahara, the universal depressant action of which has been attributed to unknown cosmic influences.

CHAPTER V.

THE INFLUENCE OF PROTEID FOOD.

It has been thought that proteid was a food which was in itself sufficient for all the requirements of the body. Pflüger[1] was able to keep a very thin dog in good condition and doing active exercise during a period of seven months, the sole diet being meat cut as free from fat as possible. Pflüger says that the fat and glycogen content of the meat ingested could not have yielded sufficient energy to provide for the action of the heart alone. It must be remembered, however, that meat is not pure proteid but is mixed with salts and water. The simplest diet capable of maintaining the body in condition is therefore a mixture of materials, or foodstuffs. Such a mixture of foodstuffs is called a food. A foodstuff is a material capable of being added to the body's substance, or one which when absorbed into the blood-stream will prevent or reduce the wasting of a necessary constituent of the organism.

The foodstuffs are:

Proteids.
Gelatinoids.
Carbohydrates.
Fats.
Salts.
Water.

A food is a palatable mixture of foodstuffs which is capable of maintaining the body in an equilibrium of substance, or capable of bringing it to a desired condition of substance. The ideal food is a palatable mixture of foodstuffs arranged together

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[1] Pflüger: "Pflüger's Archiv," 1891, Bd. l, p. 98.

in such proportion as to burden the organism with a minimum of labor. These definitions are Voit's.[1]

When proteid alone is ingested by a normal adult it is very readily burned, and is only with the greatest difficulty deposited so as to form new tissue in the organism.

In the early experiments of Bischoff and Voit, the fact is recorded that a dog weighing 35 kilograms may excrete 12 grams of urea in twenty-four hours, and the same dog after receiving 2500 grams of meat may excrete 184 grams, fifteen times as much.

Voit[2] has shown that if that quantity of meat be administered which corresponds to what is burned in starvation, nitrogen equilibrium will not be established, but some of the body's flesh will also be metabolized. This latter quantity grows steadily less if the amount of meat ingested be gradually increased until finally the point of *nitrogen equilibrium* is reached, at which the amount of meat ingested is equal to that destroyed in the body. To illustrate this Voit gives the following table, the results of work done on a dog:

MEAT ADMINISTERED.	FLESH DESTROYED.	CHANGE IN THE BODY.
0	233	—233
0	190	—190
300	379	—79
600	665	—65
900	941	—41
1200	1180	+20
1500	1446	+54

Nitrogen equilibrium was not reached until 1200 grams of meat were given, or about five times the amount of the fasting proteid metabolism.

The above experiments were made in 1858. It is no longer customary to calculate the proteid metabolism in terms of flesh destroyed, but in terms of nitrogen. The old-fashioned term flesh meant meat with a nitrogen content of 3.4 per cent. It served to illuminate the significance of metabolism at a time when few were instructed in this field of work.

E. Voit and Korkunoff[3] have published a research of sim-

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[1] Voit: Hermann's Handbuch, "Stoffwechsel," 1881, pp. 330, 344.

[2] Voit: *Ibid.*, 1881, p. 106.

[3] E. Voit and Korkunoff: "Zeitschrift für Biologie," 1895, Bd. xxxii, p. 58.

ilar character. They fed a dog with meat which had been treated with lukewarm water to remove the extractives, and which was then squeezed in a press. This process removes most of the nitrogen containing substances other than proteid. A dog will readily eat this washed meat or "proteid." The idea was to determine the minimum quantity of proteid which it was possible to ingest and still maintain nitrogen equilibrium. The different quantities of meat tabulated below were given continuously for two or three days at a time. Only the results of the last day of each of these periods are quoted:

FOOD.	N IN FOOD.	N IN EXCRETA.	DIFFERENCE.
Starvation............	0	3.996	—3.996
100 g. meat..........	4.10	5.558	—1.458
140 g. "	5.74	6.495	—0.755
165 g. "	6.77	7.217	—0.447
185 g. "	7.59	7.804	—0.214
200 g. "	8.20	8.726	—0.526
230 g. "	10.24	10.579	—0.339
360 g. "	11.99	12.052	—0.062
410 g. "	15.58	14.314	+1.266
360 g. "	13.68	13.622	+0.058
Starvation, third day..		4.026	—4.026

The figures show that nitrogen equilibrium was reached only after supplying three and a half times the amount of proteid metabolized in starvation. The authors calculate that at this time of nitrogen equilibrium the dog was still losing 28 grams of body fat, and that not much more than fifty per cent. of the total energy liberated in the organism was furnished by the proteid metabolism of the time. One may thus have nitrogen equilibrium without having carbon equilibrium.

Systems of diet for fat people are based on this knowledge. A loss of proteid is highly undesirable, while a gradual loss of adipose tissue may be a great relief to the obese.

Bornstein[1] finds that he can add proteid to his body and burn his body fat on a mixed diet containing 1600 calories with 118 grams of proteid. Such a diet contained a fuel value less than the requirement of his organism (p. 157).

If the quantity of meat ingested be steadily increased after

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[1] Bornstein: "Berliner klinische Wochenschrift," 1904, No. 46.

nitrogenous equilibrium has been reached, the proteid metabolism will gradually increase, nitrogenous equilibrium will be established at higher and higher levels, and there will be a corresponding diminution in the amount of fat burned. This was shown in the following experiment of Voit,[1] who gave different quantities of meat to a large dog weighing 30 kilograms.

INFLUENCE OF INGESTING INCREASING QUANTITIES OF MEAT.

Weights are in Grams.

Meat Ingested.	Flesh Destroyed.	Gain or Loss of Body Flesh.	Gain or Loss of Body Fat.	Respiratory Quotient.
0	165	—165	—95	.72
500	599	—99	—47	.76
1000	1079	—79	—19	.74
1500	1500	0	+4	.81
1800	1757	+43	+1	—
2000	2044	—44	+58	.84
2500	2512	—12	+57	—

Nitrogen equilibrium existed after the ingestion of 1500 grams of meat and there was also no loss of body fat (carbon equilibrium). When 2000 grams and even 2500 grams of meat were supplied it was all destroyed, as was indicated by the amount of nitrogen in the urine, but a certain quantity of carbon belonging to the ingested proteid was not eliminated in the respiration but was retained in the body. This carbon Pettenkofer and Voit believed to have been laid up in the body in the form of fat.

The respiratory quotient in the foregoing series gradually rises as would be expected from the increasing prominence of the proteid in the metabolism (p. 27). Meat alone will therefore support a dog. Rubner[2] says that a man cannot live on meat alone, not because the intestinal canal cannot digest it, but because of the physical limitations of the apparatus of mastication.

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[1] Voit: "Stoffwechsel," 1881, p. 117.

[2] Rubner: Leyden's "Handbuch der Ernährungstherapie," 1903, Bd. i, p. 42.

A subject of interest akin to the value of proteid in metabolism is that of the value of gelatin. Gelatin is a substance which contains very nearly the same quantity of nitrogen as proteid; it breaks up on chemical treatment into the same amino acids, except that it does not yield tyrosin, cystein and tryptophan. In the diabetic, gelatin yields the same amount of sugar as does proteid.[1] To what extent gelatin may take the place of proteid in the body's metabolism has long been the subject of inquiry.

It was shown first by Bischoff and Voit[2] that no matter how much gelatin was ingested it was always completely burned and some of the body's proteid in addition. Therefore gelatin never builds up new tissue, although it may somewhat diminish tissue waste. Gelatin may be formed from proteid in the body, but it cannot be reconverted into proteid nor act like proteid in metabolism. Kirchmann,[3] working in the laboratory of Erwin Voit, has shown to what extent gelatin spares proteid in metabolism. If one takes the amount of proteid metabolism in starvation as one, then the ingestion of about the same quantity of gelatin reduces the body's proteid waste 23 per cent., and if eight times this amount of gelatin be given the tissue waste may be reduced 35 per cent. In other words, the ingestion of 7.5 per cent. of the total heat requirement of the organism in the form of gelatin spares 23 per cent. of the body's proteid, while the ingestion of 60 per cent. of the requirement will only cause a decrease of 35 per cent. in proteid waste. Krummacher[4] showed that the ingestion of the full heat requirement of the animal in the form of gelatin reduced the fasting proteid metabolism by only 37.5 per cent. It is evident that no matter how much gelatin be given, tissue proteid continues to be destroyed, and it is also evident that a small quantity of gelatin has almost as great an effect as a large quantity.

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[1] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1898, vol. i, p. 395.

[2] Voit: Hermann's Handbuch, "Stoffwechsel," 1881, p. 396.

[3] Kirchmann: "Zeitschrift für Biologie," 1900, Bd. xl, p. 54.

[4] Krummacher: *Ibid.*, 1901, Bd. xlii, p. 242.

An extremely interesting experiment of Kauffmann[1] shows that when the lacking tyrosin, cystein, and tryptophan are mixed with gelatin in the proportions in which they occur in true proteid, and are given to a dog or to a man, nitrogen equilibrium may be established.

In recent years the idea has been gaining ground that proteid bodies must be broken up into amino acids before absorption in the intestine (p. 289). If this be true then ingestion of the cleavage products of proteid should maintain nitrogen equilibrium in the same way as the ingestion of meat. The first experiments in this direction were done by Loewi,[2] who gave a dog pancreas which had been self-digested until all the proteid had been converted into amino acids, as was indicated by the almost complete disappearance of the biuret reaction. Fat and carbohydrates were given with the digest, and nitrogen equilibrium was obtained and even nitrogen retention accomplished. Thus, in one experiment covering a period of eleven days, proteolytic digestive products containing an average of 6.08 grams of nitrogen were given daily, of which only 5.19 grams were eliminated in the urine, while the balance, or 0.89 gram of nitrogen, was retained in the body of the animal. This amounted to 9.79 grams of nitrogen in eleven days. Accompanying this nitrogen retention was one of 0.649 gram of phosphoric acid (P_2O_5), an amount larger than was necessary for the upbuilding of new tissue from the nitrogen compounds retained. Loewi concluded that he had demonstrated the synthesis of new proteid within the organism.

Lesser[3] gave a pancreatic digest of fibrin to a dog and was unable to obtain nitrogen equilibrium.

Henderson and Dean[4] confirmed Loewi in finding that they could obtain nitrogen equilibrium by feeding a dog with the

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[1] Kauffmann: "Pflüger's Archiv," 1905, Bd. cix, p. 440.

[2] Loewi: "Archiv für ex. Path. und Pharm.," 1902, Bd. xlviii, p. 303.

[3] Lesser: "Zeitschrift für Biologie," 1904, Bd. xlv, p. 506.

[4] Henderson and Dean: "American Journal of Physiologie," 1903, vol. ix, p. 386.

cleavage products of meat produced by treatment with sulphuric acid.

Stiles and Lusk,[1] on the contrary, gave a fasting diabetic dog a pancreatic digest of meat which had undergone fourteen months of proteolytic cleavage, and observed that the nitrogen of it was completely eliminated in the urine without protecting the body from loss of proteid, which would have occurred had meat itself been administered.

To reconcile these differences it seemed necessary to consider the differences in methods of preparing the end products of the proteid to be ingested. Indeed, Abderhalden and Rona[2] find that mice live on casein split with pancreatin as long as they do on casein alone; whereas they die much earlier if the casein has been submitted to peptic and then pancreatic digestion, or if it has been broken up by acid hydrolysis. Henriques and Hansen[3] also find that casein broken up by acid will not maintain nitrogen equilibrium in rats, but that if the pancreas of the ox and a small piece of the intestine of the dog (to furnish erepsin) be digested for two months at 40°, and the resulting material given to rats, nitrogen equilibrium will be maintained. The authors further find that the monoamino acid fraction (the filtrate after precipitation with phosphowolframic acid), and also the alcoholic extract of the last-named digest, maintains rats in nitrogen equilibrium. The residue left after alcoholic extraction will not do so.

Finally Abderhalden and Rona[4] have accomplished a most interesting experiment upon a dog. The animal was given daily a constant quantity of non-nitrogenous foods which were: fat, 25 grams; starch, 50 grams; cane sugar, 10 grams; dextrose, 5 grams. The dog was brought into nitrogen equilibrium by giving meat containing 2 grams of nitrogen. Then for this were substituted the amino cleavage products of casein, pro-

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[1] Stiles and Lusk: "American Journal of Physiology," 1903, vol. ix, p. 380.

[2] Abderhalden and Rona: "Zeitschrift für physiologische Chemie," 1904, Bd. xlii, p. 528.

[3] Henriques and Hansen: *Ibid.*, 1905, Bd. xliii, p. 417.

[4] Abderhalden and Rona: *Ibid.*, 1905, Bd. xliv, p. 198.

duced by pancreatic digestion and also containing 2 grams of nitrogen. During sixteen days on this diet there was an average daily gain of 0.12 grams of nitrogen by the dog. Then casein hydrolized by acid and containing 2 grams of nitrogen was administered for ten days, during which time the dog lost 0.48 grams of nitrogen daily. Amino products prepared after this fashion will therefore not preserve nitrogen equilibrium. Lastly, the diet was continued without any nitrogenous food. The daily waste of body nitrogen was then 0.53 grams. The loss was the same as when the casein hydrolized by acid was ingested, indicating that this particular array of cleavage products had no protecting power over the body proteid.

The absence of virtue in the casein hydrolized by acids is attributed by Abderhalden and Rona[1] to the complete destruction of all polypeptids (p. 293) which are probably the constructive nuclei (Bausteine) of proteid. When the latter are present a partial reconstruction of amino acids into the proteids of blood serum is possible.

It seems therefore proved that amino bodies resulting from certain proteolytic cleavages may be the equivalent in metabolism of ingested proteid itself.

In practical dietetics these substances can have no value, as they tend to produce diarrhea, as do also albumoses and peptones when given in any quantity.[2] As illustrating this, Cohnheim[3] finds that though somatose is more digestible than meat, still over 30 grams is undesirable in the daily diet of a man.

The effect of copious drinking of water upon proteid metabolism has been made the subject of various studies. A small increase in nitrogen elimination has usually been noted. This was first established by Voit, who explained it as due to an increased circulation which influenced the flow of the intra-

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[1] Abderhalden and Rona: "Zeitschrift für physiol. Chemie," 1906, Bd. xlvii, p. 397.

[2] Voit: "Münchener med. Wochenschrift," 1899, Nos. 6 and 7.

[3] Cohnheim: "Pflüger's Archiv," 1904, Bd. cvi, p. 17.

cellular fluids. Heilner[1] has recently shown that giving 2000 c.c. of water to a fasting dog on two successive days raises his urinary nitrogen from 3.15 grams to 4.09 and 3.58 grams on the two days of water ingestion, and then the nitrogen excretion falls to 2.22 and 2.62 on the following days. In this experiment the carbon dioxid excretion was very slightly increased and the temperature of the dog was not affected. The quantity of urine rose from 90 c.c to 2050 c.c.

Straub[2] found that an extra ingestion of 2000 c.c. of water in a man who was in nitrogen equilibrium on a diet containing 20.56 grams of nitrogen had no effect on proteid metabolism; whereas Hawk[3] who gave less proteid nitrogen but more water, found that the ingestion of 4500 c.c. of water caused the urinary nitrogen to rise from 11.03 to 12.48 on the first day, and 11.82 on the second day, with a fall to 10.91 grams on the succeeding day when no water was given. Hawk interprets the action of copious water drinking as twofold,—*first*, to cause a removal of any accumulation of nitrogenous decomposition products from the organism, as was indicated by the greater increase of 12.8 per cent. in the nitrogen elimination of the first day; and, *second*, to cause a true increase in proteid metabolism as was indicated by the smaller increase of 6.8 per cent. on the second day of water ingestion.

One of the striking characteristics of starvation metabolism was shown to be its extreme regularity from hour to hour and from day to day. What, then, is the hour-to-hour metabolism after meat ingestion?

The classical experiments of Voit[4] and of Feder[5] have been more fully worked over by Gruber. Gruber[6] fed a dog with 500, 1000 and 1500 grams of meat on different days. He collected the urine every two hours after the meal and determined

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[1] Heilner: "Zeitschrift für Biologie," 1906, Bd. xlvii, p. 541.

[2] Straub: *Ibid.*, 1899, Bd. xxxvii, p. 527.

[3] Hawk: "University of Pennsylvania Medical Bulletin," March, 1905.

[4] Voit: "Physiologische Untersuchungen," Augsburg, 1857, p. 42.

[5] Feder: "Zeitschrift für Biologie," 1881, Bd. xvii, p. 541.

[6] Gruber: *Ibid.*, 1902, Bd. xlii, p. 421.

the nitrogen output. The curves of nitrogen elimination under these circumstances are as follows:

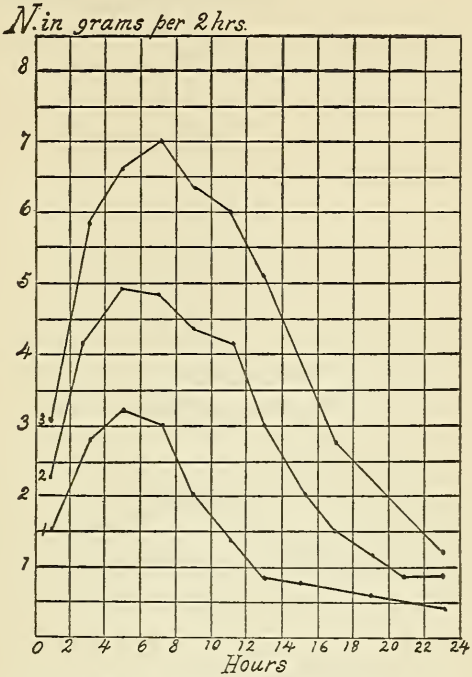

Fig. 5.—1, after 500 g. meat + 50 g. fat + 350 c.c. water; 2, after 1000 g. meat + 200 c.c. water; 3, after 1500 g. meat + 500 c.c. water. On each of these days the animal was in nitrogen equilibrium.

It is evident that there is an early elimination of proteid nitrogen which here reaches a maximum between five and seven hours after feeding, and that the hour of the maximum excretion is delayed by increasing the quantity of meat ingested.

It is apparent, therefore, that the proteid metabolism as illustrated by the curve of nitrogen elimination is quite different from the even metabolism of starvation.

If we turn from the nitrogen elimination to that of the carbon in the respiration, it will be found that here the elimination is comparatively even. Frank and Trommsdorf[1] gave a dog 1191 grams of meat which had been freed from extractives

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[1] Frank and Trommsdorf: "Zeitschrift für Biologie," 1902, Bd. xliii, p. 266.

by means of lukewarm water. The nitrogen and carbon of the urine and feces, and the carbon of the respiration were determined, and from these data the proteid and fat metabolism were calculated in the usual manner. From this the heat produced was estimated. The essential results were thus tabulated:

VARIATION IN METABOLISM AFTER MEAT INGESTION.

Period.	No. of Hours.	Per Hour.		
		N in Urine.	C in Respiration.	Calories from Metabolism.
Starvation	24	0.1944	2.968	36.72
Meat Ingested:				
First period after meat	4 h. 9 m.	0.917	3.862	43.94
Second " " "	3 h. 14 m.	1.373	3.886	41.53
Third " " "	5 h. 44 m.	1.592	3.872	41.00
Fourth " " "	10 h. 53 m. (night)	1.064	3.493	38.46

It is evident that while the curve of the nitrogen elimination shows a maximum rise to nearly eight times that of fasting and varies greatly, the carbon curve is much more even and is not much above that found in starvation. The maximum rise in heat production occurs in the first four hours after the ingestion of meat and amounts to twenty per cent. The heat production falls during the night hours.

Rubner[1] has obtained similar results after giving 460 grams of washed meat to a dog weighing 24 kilograms. His calculations show the following metabolism during six-hour periods:

VARIATION IN METABOLISM AFTER MEAT INGESTION.

First Day of Ingestion.				
Time of Day.	N in Urine.	Cal. from Proteid.	Cal. from Fat.	Calories Total.
Day, 9–3	5.06	135.1	143.9	279.0
3–9	6.11	163.0	85.2	248.2
Night, 9–3	4.64	123.8	105.4	229.2
3–9	2.76	73.6	169.5	243.1
Total	18.6	495.5	504.0	999.5

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[1] Rubner: "Gesetze des Energieverbrauchs," 1902, p. 365.

VARIATION IN METABOLISM AFTER MEAT INGESTION
(*Continued*).

Third Day of Ingestion.

Time of Day.	N. in Urine.	Cal. from Proteid.	Cal. from Fat.	Calories Total.
Day, 9–3..........	5.57	148.7	130.4	279.1
3–9..........	8.94	238.7	33.4	272.1
Night, 9–3..........	5.32	142.0	76.3	218.3
3–9..........	2.66	71.0	162.4	233.4
Total............	22.5	600.4	402.5	1002.9

The nitrogen curve varies. The total heat production is greatest during the hours immediately following the ingestion of proteid, but is otherwise comparatively even.

If we pass from the consideration of proteid metabolism, as indicated by the nitrogen curve, to the consideration of the intermediary metabolism of proteid we can see more clearly that the curve of proteid nitrogen excretion is not a true index to the sum of the activities contributed to the cells by proteid metabolism.

Voit[1] believed that there was an early cleavage of the proteid molecule into a nitrogenous portion and a non-nitrogenous portion, a cleavage involving the liberation of only a small amount of energy; that there was a rapid combustion of the nitrogenous radicle, as shown by the elimination of the nitrogenous end-products in the urine; and that the non-nitrogenous radicle which contained the major part of the potential energy of the proteid molecule might in part be temporarily stored either as glycogen or fat and be gradually doled out to the tissues as the need required.

Claude Bernard believed that glycogen could arise from proteid. Wolffberg[2] let fowls fast two days to remove the glycogen and then for two days gave meat powder which was

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[1] Voit: "Zeitschrift für Biologie," 1891, Bd. xxviii, p. 291.

[2] Wolffberg: *Ibid.*, 1876, Bd. xii, p. 278.

free from carbohydrate. Two fowls, killed during the interval of proteid digestion, showed considerable glycogen in their livers (1.56 and 1.45 per cent.) and muscles (0.251 and 0.454 per cent.), much more than would have been present in starvation. Two similar fowls, killed seventeen and twenty-four hours after the last proteid ingestion, contained much less glycogen in their livers (0.145 and 0.22 per cent.) and muscles (0.211 and 0.162 per cent.). This origin of glycogen from proteid was fully confirmed by Külz[1] in a very extended series of experiments in which chopped meat, fully extracted with warm water, was made the basis of the ingesta. It became evident from these experiments that if sufficient proteid were given to an animal, part of the proteid carbon could be retained as glycogen.

It has long been believed that sugar arises from proteid in diabetes. Kossel[2] first suggested that hexone bases, leucin, and other proteid end-products, contained six atoms of carbon as did also the ordinary hexose sugars, such as dextrose, levulose and galactose. The theory of the origin of sugar in diabetes from these amino products was strongly advocated by Friedrich Müller.[3] The definite proof of this was afforded by Stiles and Lusk[4] who gave a mixture of amino bodies prepared by the pancreatic proteolysis of meat to a dog rendered diabetic with phlorhizin. The mixture was free from proteid. The nitrogen ingested was entirely eliminated in the urine, and for each gram of such nitrogen 2.4 grams of extra sugar appeared in the urine.

A little farther on it will be shown how such a body as leucin of the general formula C_6NH_2 may be denitrogenized[5] and in part converted into dextrose (p. 232). Knopf[6] has shown that

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[1] Külz: "Ludwig's Festschrift," 1890, p. 83.

[2] Kossel: "Deutsche medizinische Wochenschrift," 1898, p. 58.

[3] Müller and Seeman: *Ibid.*, 1899, p. 209.

[4] Stiles and Lusk: "American Journal of Physiology," 1903, vol. 9, p. 380.

[5] Halsey: "American Journal of Physiology," 1904, vol. x, p. 229.

[6] Knopf: "Archiv für ex. Path. und Pharm.," 1903, Bd. xlix, p. 123.

other amino bodies, like asparagin, which do not contain six atoms of carbon are likewise convertible into dextrose in the body. (See chapter on Diabetes.) Considerable sugar may therefore originate from proteid in the course of its ordinary metabolism. The question arises at what time during the metabolism does this sugar become available for combustion in the organism? This question was answered by an experiment of Reilly, Nolan, and Lusk.[1] These authors gave a fasting phlorhizinized dog 500 grams of meat and collected the urine in two 3- and one 6-hour periods. The results were as follows:

EXCRETION OF DEXTROSE AND NITROGEN BEFORE AND AFTER INGESTING 500 GRAMS OF MEAT IN DIABETES.

	DEXTROSE.	NITROGEN.	D:N.
Preceding 3 hours	5.96	1.75	3.41
First 3 hours after feeding	12.43	2.52	4.92
Second 3 " " "	14.70	3.76	3.91
Third 3 " " "	11.23	3.85	2.92
Fourth 3 " " "	11.23	3.85	2.92
Following 3 hours	6.34	1.78	3.56

The normal fasting relation between dextrose and nitrogen changed immediately upon the ingestion of meat. During the first hours more dextrose was eliminated than corresponded to the nitrogen in the urine. During the later hours this proportion was reversed. The sugar elimination therefore took place decidedly before that of the nitrogen. This is shown in the following calculation of the percentage elimination of nitrogen and dextrose in 3-hour periods following the ingestion of 500 grams of meat in the above experiment:

	DEXTROSE.	NITROGEN.
During first 3 hours	26.06	18.02
" second 3 "	29.64	26.90
" third 3 "	22.65	27.54
" fourth 3 "	22.65	27.54
	100.00	100.00

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[1] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1898, vol. i, p. 395.

The relations are represented in the following curve:

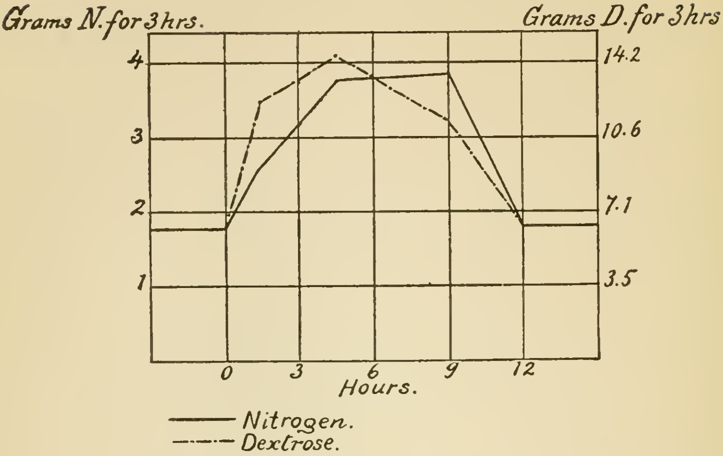

Fig. 6.—Curve showing the elimination of dextrose before nitrogen after meat ingestion (500 grams) in diabetes.

That the dextrose production from the meat ingested was proportional to the proteid destroyed is evident from the following comparison, in which the sum of the dextrose and nitrogen eliminated in the twelve hours is considered. Nitrogen and dextrose double in quantity after the ingestion of meat, but their relative amount remains the same as in starvation.

	Dextrose.	Nitrogen.	D : N.
Fasting 12 hours....................	23.87	7.00	3.41
After 500 g. meat, 12 hours.........	49.59	14.00	3.54
Subsequent 12 hours................	25.36	7.11	3.56

The curve shows that there is an early production of sugar from proteid which may be liberated in metabolism before the nitrogen belonging to the proteid is eliminated in the urine. A similar early production of sugar from proteid has also been observed after feeding dogs with meat in pancreas diabetes.[1]

Since one gram of nitrogen in the urine represents a destruction of 6.25 grams of meat proteid, and since there is simultane-

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[1] Berger: Inaugural Dissertation, Halle (Nebelthau), 1901; cited from Maly's "Jahresbericht über Thierchemie," Bd. xxxi, p. 848.

ously an average elimination of 3.65 grams of dextrose in phlorhizin diabetes, it may be calculated that the sugar production from meat amounts to 58 per cent. by weight of the meat proteid metabolized and may contain 52.5 per cent. of its total available energy (p. 64).

After the ingestion of proteid in the normal organism this sugar early becomes available and may be burned before the nitrogen belonging to it is eliminated, or if the sugar be formed in excess, it may be stored as glycogen in the liver and muscles of the body for subsequent use. In this way it is obvious that at least half the energy in proteid may be independent of the curve of nitrogen elimination, but may rather act as though it had been ingested in the form of carbohydrate. Carbohydrates when ingested do not cause a rise in the production of heat, but may simply burn as needed by the cells. This will be explained in the next chapter. It is therefore evident that this carbohydrate, which is early supplied in the breaking down of proteid, may distribute its energy according to the requirement of the cells as long as it lasts. This is apparently the principal cause of the evenness of the carbon dioxid excretion as contrasted with the great irregularity of the nitrogen elimination after proteid ingestion.

It has been noted that Frank and Trommsdorf, and Rubner also, in experiments previously mentioned, calculated the heat production during the first few hours after feeding with meat according to the usual method from the data furnished by the nitrogen and carbon elimination. This, however, will not tell the exact truth regarding the fat and proteid metabolism during a short period, for dextrose from proteid may be burning, which is not indicated by the nitrogen excretion of the time. The error here introduced would not be large, but a correction would tend to reduce somewhat the calculated heat production during the period immediately following the ingestion of meat. This experiment should be controlled by simultaneous measurements with an animal calorimeter. It is obvious that respiration experiments extending over a few hours cannot so accurately present the picture of the metabolism after feeding with meat as they do in the case of starvation, where the intermediary metabolism is a constant and even factor.

Concerning the intermediate metabolism of proteid, it is further shown from the work of Parker and Lusk[1] that the ingestion of casein by rabbits maintained under the influence of benzoic acid results in an elimination of hippuric acid which is proportional to the proteid metabolism. This is illustrated in the following table:

CONSTANT RELATION BETWEEN GLYCOCOLL PRODUCTION AND N ELIMINATION AFTER INGESTING PROTEID.

DAY.	CASEIN INGESTED IN GRAMS.	BENZOIC ACID GIVEN IN GRAMS.	GRAMS HIPPURIC ACID EXCRETED.	TOTAL N EXCRETED IN GRAMS.	HIPPURIC ACID N: TOTAL N.
First	4	1	.7230	1.469	1:25.9
Second	5	1	.7575	1.456	1:24.6
Third	10	1.5	1.0302	1.929	1:23.9

Total nitrogen and hippuric acid output maintain the same ratio throughout the above experiment.

It may be estimated that casein yields 3.45 per cent. of glycocoll in metabolism as compared with 3.98 per cent. obtained when body proteid metabolizes in starvation (p. 64). This experiment seems remarkable because the chemist has not been able to obtain glycocoll from casein.

Magnus-Levy,[2] apparently using the same method, finds that 25 to 27 per cent. of the total urinary nitrogen of rabbits fed with cream and of a goat fed with hay is excreted in the form of hippuric acid. He calculated that only 4 per cent. of this could have been derived from glycocoll preformed in the proteid metabolized, but that 20 per cent. could have originated from leucin in passing through a glycocoll stage. Why Parker and Lusk obtained the 4 per cent. elimination and Magnus-Levy secured one of 25 per cent. is not at present clear.

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[1] Parker and Lusk: "American Journal of Physiology," 1900, vol. iii, p. 472.

[2] Magnus-Levy: "Münchener med. Wochenschrift," 1905, Bd. lii, p. 2168.

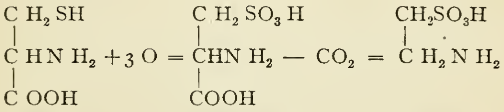
The writer has unsuccessfully endeavored to bring about an elimination of cystein, the sulphur-containing compound in the proteid complex, by constant treatment of a dog with benzol chlorid. It is possible that the bromid or iodid might be successfully used.

Since the last sentence was written the work of Wolf[1] has been published, which shows that after frequent administration of benzol bromid to a dog, an artificial cystinuria is brought about. The benzol bromid unites with the cystein liberated in proteid metabolism and the compound, a mercapturic acid, is eliminated in the urine. In this way Wolf increased fourfold the unoxidized sulphur (cystein-S) in the urine, and nearly removed all the inorganic sulphate from the urine, although curiously enough there was a slight increase in the quantity of ethereal sulphates present. Folin and Alsberg[2] investigated a case of cystinuria and found similar relations. The increase in neutral sulphur was at the expense of alkaline sulphate in the urine. The cystein elimination was increased by increasing the proteid in the food.

Friedmann[3] shows that the cystein of mercapturic acid is the same cystein as may be obtained on the cleavage of proteid in the laboratory.

If cystein be administered to a normal person it is burned and does not alter the normal relation between oxidized and unoxidized sulphur in the urine.[4]

That cystein is the mother substance of the taurin of the bile Friedmann[5] illustrates in accordance with the following formulæ:



$$\begin{array}{lclcl} CH_2SH & & CH_2SO_3H & & CH_2SO_3H \\ | & & | & & | \\ CHNH_2 + 3\,O & = & CHNH_2 - CO_2 & = & CH_2NH_2 \\ | & & | & & \\ COOH & & COOH & & \end{array}$$

Cystein. Cysteinic acid. Taurin.

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[1] Mariott and Wolf: "American Medicine," 1905, vol. ix, p. 1026.

[2] Folin and Alsberg: "American Journal of Physiology," 1905, vol. xiv, p. 54.

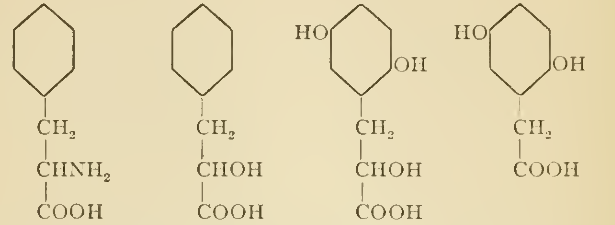
[3] Friedmann: "Hofmeister's Beiträge," 1904, Bd. iv, p. 486.

[4] Blum: *Ibid.*, 1904, Bd. v, p. 1.

[5] Friedmann: *Ibid.*, 1902, Bd. iii, p. 1.

The indications are that cystein is a normal product of proteid metabolism which a patient suffering from cystinuria is unable to burn.

In a phenomenon called alcaptonuria tyrosin and phenylalanin are oxidized only as far as the alcaptonic acids, which are uroleucinic and homogentisic acids, and in this form they appear in the urine. Their production from phenylalanin according to Falta[1] is as follows:



Phenylalanin. Phenyl-α-lactic acid. Uroleucinic acid. Homogentisic acid.

He finds that if phenylalanin or tyrosin are administered in alcaptonuria, they are completely converted into the alcaptonic acids and so eliminated. In alcaptonuria the ratio between homogentisic acid and nitrogen elimination in the urine is constant, being 45:100[2] while the distribution of the various other nitrogenous compounds in the urine remains normal. Garrod and Hale[3] find the same ratio as above and believe with Falta that where this error in normal metabolism occurs it is complete in the sense that the homogentisic acid excreted represents the whole of the tyrosin and phenylalanin of the proteids broken down.

Neubauer and Falta[4] have recently emphasized the idea that the alcaptonic acids are always formed in normal metabolism, but in this rare disease cannot be further oxidized.

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[1] Falta: "Biochemisches Centralblatt," 1904, Bd. iii, p. 175.

[2] Langstein and Meyer: "Deutsches Archiv für klin. Med.," 1903, Bd. lxxviii; Schumm: "Münchener med. Wochenschrift," 1904, Bd. xxxvi, p. 1599.

[3] Garrod and Hale: "Journal of Physiology," 1905, vol. xxxiii, p. 205.

[4] Neubauer and Falta: "Zeitschrift für physiologische Chemie," 1904, Bd. xlii, p. 81.

Sugar, glycocoll, cystein, and the alcaptonic acids are therefore products of proteid metabolism whose excretion may be brought about by special means or by certain pathological conditions.

Kynurenic acid, which is frequently found in dogs' urine, has acquired new interest since Ellinger's[1] discovery that if a dog be given tryptophan—a product of proteolysis—the kynurenic acid is greatly increased in the urine. Mendel and Jackson[2] found that the kynurenic acid elimination in dogs varied directly with the proteid metabolism but was not derived from gelatin metabolism. Ellinger[3] has fed a rabbit, whose urine normally contains no kynurenic acid, with tryptophan, and found kynurenic acid in the urine. Rabbits, however, normally burn kynurenic acid when ingested in small amounts. He reaches the conclusion that animals in general may produce kynurenic acid from tryptophan in proteid metabolism, and that this is usually readily oxidized, except in the organism of the dog, where it is only partly destroyed and therefore appears in the urine.

There is a nitrogenous end-product normally present in the urine the origin of which is obscure, and this is creatinin.

Voit[4] found that while muscle contained creatin, the urine if it were acid contained creatinin; otherwise creatin appeared. Urinary acid phosphate causes the dehydration of creatin into creatinin in the kidney. Voit showed that ingested creatin was completely eliminated in the urine, and that the amount in the urine after meat ingestion was the quantity contained in the meat metabolized.

Following this line of research, Gruber[5] gave a dog 1500 grams of meat daily and noticed the constancy of the relation between the total nitrogen and creatinin in the urine. There was no relatively increased creatinin elimination during starvation

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[1] Ellinger: "Zeitschrift für physiologische Chemie, "1904, Bd. xliii, p. 325.

[2] Mendel and Jackson: "American Journal of Physiology," 1898, vol. ii, p. 1.

[3] Ellinger: *Loc. cit.*

[4] Voit: "Zeitschrift für Biologie," 1868, Bd. iv, p. 77.

[5] Gruber: Voit's Festschrift, "Zeitschrift für Biologie," 1901, Bd. xlii, p. 416.

following on a period of excessive ingestion of meat which showed that creatin had not been stored up in the body.

The results of these experiments are as follows:

CREATININ ELIMINATION AFTER MEAT INGESTION.

Day.	Food.	N in Urine.	Creatinin in Urine.	Creatinin : N.
First........	1500 g. meat.	41.20	3.916	1 : 10.52
Second......	"	47.60	4.119	1 : 11.55
Third.......	"	45.67	4.054	1 : 11.26
Fourth......	starvation.	11.35	0.478	1 : 23.74
Fifth........	"	6.97	0.469	1 : 14.85
Sixth........	"	5.98	0.569	1 : 10.53

The complete elimination of ingested creatin observed by Voit has been fully confirmed by Mallet.[1]

Creatin, therefore, is not a precursor of urea, since it passes through the organism unchanged. Nor does the amount of urea produced influence the elimination of creatinin. Folin[2] has recently shown that on a creatin-free diet (such as milk and cream) the amount of creatinin-nitrogen in the urine is 0.6 gram, whether the total nitrogen in the urine be 16.8 or 3.6 grams. Folin regards this small quantity of creatin as a constant product of the essential breakdown of living cell proteid (p. 293).

Ph. Munk[3] says that in convalescence the required amount of creatin is retained for the upbuilding of new tissue. Creatinin is absent in the urine of milk-fed children,[4] presumably for the same reason. It would be interesting in the light of Folin's work to see whether on a milk diet in convalescence creatinin would disappear from the urine. Its absence would confirm Munk's theory. Cellular metabolism may perhaps prepare for new muscle protoplasm a constituent not immediately derivable from the milk casein.

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[1] Mallet: U. S. Dept. of Agriculture, 1899, Bulletin 66.

[2] Folin: "American Journal of Physiology," 1905, vol. xiii, p. 117.

[3] Munk: "Deutsche Klinik," 1862, p. 300.

[4] Rietschel: "Jahrbuch für Kinderheilkunde," 1905, Bd. xli, p. 4.

Creatin is the extractive existing in larger quantity than any other in muscle. It is one of the principal constituents of Liebig's extract of beef. Such an extract, which contains also xanthin, is not strictly a food, since its constituents are largely ready for elimination in the urine.[1] Bürgi[2] shows that if meat extract be administered it is excreted in the urine excepting 4.57 per cent. of its nitrogen, 14.85 per cent. of its carbon, and 17.55 per cent. of its energy content.

Its value lies in its *flavor*, which promotes the proper flow of the digestive juices.[3]

It may be incidentally remarked that the principal value of "patent" foods lies in their flavor. If agreeable to the taste of the individual they usually afford a harmless indulgence. That beef, milk, cream, butter, and rice are equally suitable for all the purposes of proper living is a fact not sufficiently advertised. The old-time fraud of "patent" foods being "brain restorers" is as foolish a lie as can be written.

Rubner[4] says that the rise of the curve of sulphur elimination precedes that of nitrogen, while that of the phosphate elimination follows it. The experiment is on the dog already described (page 109) during the 6-hour periods following an ingestion of 460 grams of washed meat. The following represents the percentage elimination of nitrogen, sulphur and phosphorus during 6-hour intervals on the third feeding day. Of 100 per cent. there were excreted:

	N.	S.	P_2O_5.
During the first 6 hours	24.8	36.7	16.0
" second 6 "	39.8	31.7	32.1
" third 6 "	23.6	21.1	33.4
" fourth 6 "	11.8	10.5	18.5

Sherman and Hawk,[5] however, give curves showing beauti-

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[1] Rubner: "Zeitschrift für Biologie," 1883, Bd. xix, p. 343.

[2] Bürgi: "Archiv für Hygiene," 1904, Bd. li, p. 1.

[3] Voit: "Stoffwechsel," 1882, p. 449.

[4] Rubner: "Energiegesetze," 1902, p. 368.

[5] Sherman and Hawk: "Am. Jour. of Physiology," 1900, vol. iv, p. 43.

fully an almost parallel elimination of sulphur and nitrogen in man on a mixed diet. A curve showing this is here presented:

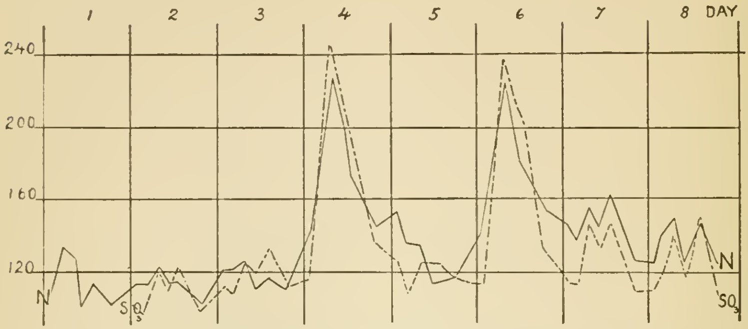

Fig. 7.—The curves here shown represent the relative fluctuations in the average rates of excretion of nitrogen and SO_3. The values on the left represent percentages of an assumed standard rate of excretion for each of these constituents. It will be seen that in general the excretion of sulphates ran quite closely parallel to that of nitrogen.

This discussion of the elimination of various intermediary products of proteid metabolism lifts the veil from hidden factors sufficiently to give a glimpse into a field of increasingly fruitful investigation.

A question which has aroused great interest has been that concerning the production of fat from proteid. Pettenkofer and Voit[1] found that after ingesting considerable quantities of proteid, although the nitrogen of the proteid was eliminated in the urine, a part of the carbon was retained in the body and not excreted by the usual channels. They estimated that meat proteid contained 3.68 grams of carbon to each gram of nitrogen. If less than 3.68 grams of carbon appeared in the total excreta when one gram of nitrogen was eliminated, then some proteid carbon must have been stored in the body. This carbon might have been retained in two forms—as glycogen or as fat. Claude Bernard had shown that glycogen increases in the liver after the ingestion of proteid. The retained carbon as ob-

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[1] Pettenkofer and Voit: "Annalen der Chemie und Pharm.," 1862, II Supplement, pp. 52 and 361.

served by Pettenkofer and Voit was in such large quantity as to preclude the possibility of its retention entirely as glycogen, and therefore they concluded that fat must have been prepared from proteid and stored up in the body. This afforded an experimental basis for the theory of a production of fat from proteid in fatty degeneration.

Later Rubner,[1] in Voit's laboratory, showed that the relation 3.68 C: 1 N in proteid, as used by Pettenkofer and Voit, was erroneous, and that meat fully extracted with ether contains only 3.28 of carbon to one of nitrogen. The polemical arraignment by Pflüger[2] of Voit's older work was based upon these results of Rubner. Instead of there being a great retention of proteid carbon, there was none in some experiments and very little in others. The formation of fat from proteid was evidently less easy of demonstration than it had seemed.

The subject was investigated anew by Cremer,[3] who starved a cat for many days, and then gave the animal all the lean meat it would eat, or about 450 grams a day. The cat was kept in a respiration apparatus and the total excreta were collected. The carbon belonging to the meat ingested was calculated at the low ratio of 3.18 to 1 of nitrogen. The average daily metabolism during the eight days of meat ingestion is indicated in the following table:

WEIGHTS IN GRAMS.

N in urine and feces,	C in			Meat C calculated from N excreted,	C from meat added to the body,
	Urine,	Feces,	Respiration,		
13.0	7.5	1.4	25.4	41.6	7.3
		34.3			

There was a daily excretion of 13 grams of nitrogen corresponding to the liberation of 41.6 grams (13 × 3.18) of proteid carbon. But only 34.3 grams of carbon were actually eliminated from the body, and a difference of 7.3 grams was re-

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[1] Rubner: "Zeitschrift für Biologie," 1885, Bd. xxi, p. 324.

[2] Pflüger: "Pflüger's Archiv," 1892, Bd. lii, p. 239.

[3] Cremer: "Zeitschrift für Biologie," 1899, Bd. xxxviii, p. 309.

tained in the body; 17.5 per cent. of the proteid carbon therefore was not eliminated. For eight days the whole carbon retention was 58 grams, which corresponds to a glycogen production of 130 grams. The cat, however, contained only 35 grams of glycogen, determined after killing it at the end of the experiment. The balance of the carbon must have been stored as fat.

Cremer[1] notes that a cat fed as above contains 1.47 per cent. of muscle glycogen, which is as much as the maximum (1.37 per cent.) found by E. Voit in geese after the ingestion of starch.

Since it is known that sugar in excess may be converted into body fat and that meat may yield 58 per cent. of sugar in metabolism, there is every reason to believe that if proteid be ingested in excess this sugar may be converted into glycogen and then, if the quantity be sufficient, into fat.

It is quite possible that the origin of fat from proteid is in its nature the same as the origin of fat from carbohydrates.

Rubner[2] has noted a similar carbon retention after the ingestion of proteid in excess. Two examples of this may be cited.[3]

The first experiment was upon a dog which had been reduced by starvation from a weight of 11 to 6 kilograms. He was then given 500 grams of meat a day.

CARBON RETENTION AFTER PROTEID INGESTION.

DAY.	FOOD.	N IN EXCRETA.	C FROM FAT METABOLISM.	CALORIES FROM PROTEID.	CALORIES FROM FAT.	TOTAL CAL. FROM METABOLISM.	BODY WEIGHT
First	Starvation.	1.31	22.46	32.75	275.2	308.0	5.94
Second	Starvation.	1.52	19.77	38.00	243.2	281.2	5.82
Third	500 g. meat.	13.05	(—0.87)	339.3	—8.9	330.4	5.86
Fourth	500 g. meat.	14.20	(—2.41)	355.0	—24.9	330.1	6.00

This experiment shows that on the first day of meat ingestion 0.87 gram of carbon from proteid was retained in the dog and on

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[1] Cremer: "Zeitschrift für Biologie," 1899, Bd. xxxviii, p. 313.

[2] Rubner: "Gesetze des Energieverbrauchs," 1902, pp. 57, 84.

[3] For a third example see this book, table on p. 128.

the second day 2.41 grams were so retained. Rubner[1] has calculated that the carbon in the respiration derived from proteid has a calorific value of 10.2 calories per gram. When proteid carbon is retained in the body, its heat equivalent must be deducted from the heat value of the proteid metabolism as computed from the nitrogen in the excreta, in order to obtain the true total of heat liberated. This heat value of retained carbon is a little above the calorific value of carbon in dextrose, which is 9.4 calories per gram.

The second experiment which may be cited was done by Rubner upon a large dog which was given 2000 grams of meat at a time. The results were as follows:

CARBON RETENTION AFTER PROTEID INGESTION.

Day.	Food.			Excreta.		Calories.		
	Kind.	N.	Cal.	N.	Fat C.	Proteid.	Fat.	Total.
First	Starv.			5.01	48.19	125.75	592.72	718.49
Second	Starv.			5.10	49.90	128.00	613.77	741.77
Third	2000 g. meat.	68	1926	51.60	(—29.58)	1351.9	—305.66	1046.34
Fourth	Starv.			12.39	37.19	325.62	420.54	746.16
Fifth	2000 g. meat.	68	1926	52.68	(—26.58)	1380.22	—274.57	1105.65
Sixth	Starv.			12.18	36.82	319.12	452.89	772.01

On both days when 2000 grams of meat were ingested, carbon was retained in the organism either as glycogen or fat. On the first of these days 17.7 per cent. of the total proteid carbon was retained, which corresponds to 17.5 per cent. found by Cremer in the cat during a prolonged period of proteid diet. The writer, on the basis of his work on diabetes, computes that 44 per cent. of the total carbon in meat proteid may be converted into dextrose (p. 112). It is known that sugar is convertible into fat (p. 150). If 44 per cent. of proteid carbon may be converted into dextrose and under other conditions 17.5 per cent. may be converted into fat, it is evident that of the total dextrose-carbon which may be produced in proteid metabolism,

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[1] Rubner: "Zeitschrift für Biologie," 1885, Bd. xxi, p. 363.

40 per cent. can be converted into fat-carbon (p. 151). There seems to be no doubt that proteid may in part be converted first into glycogen and then into fat after excessive proteid ingestion. The question of a "fatty degeneration" of proteid under pathological conditions is another matter and will be considered at another time. (See Chapter XII.)

These last two experiments of Rubner's bring to light a very striking change in the metabolism after the ingestion of proteid in excess. The total heat production is markedly increased. To what may this be due?

Mering and Zuntz[1] believed that such increased metabolism was due to the activity of the intestinal tract after the ingestion of food.

Voit[2] criticised this view and said that a rise in the carbon dioxid excretion, from 366 grams in starvation to 783 grams after ingestion of meat in excess, was too great to be due to intestinal activity, and, indeed, corresponded to the rise noted only after the hardest exercise. Furthermore, Voit had shown that after giving a medium quantity of fat, the carbon dioxid excretion and oxygen absorption were almost the same as in hunger, notwithstanding the activity of the filled intestine.

This question has received very painstaking and elaborate investigation at the hands of Rubner, who has published his results in a book entitled "Die Gesetze des Energieverbrauchs bei der Ernährung." This volume is an extension of a work of which a preliminary communication was published by Rubner[3] from Voit's Munich laboratory in 1885. During subsequent years of continued activity the doctrines were more and more firmly established.

Rubner shows that bones given to a dog will not increase his metabolism, in spite of the intestinal irritation, so the increase after meat ingestion is not due to a nerve reflex of mechanical

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[1] Mering and Zuntz: "Pflüger's Archiv," 1877, Bd. xv, p. 634.

[2] Voit: "Physiologie des allegemeinenen Stoffwechsel," 1881, p. 209.

[3] Rubner: "Sitzungsberichte d. kgl. bayr. Acad. d. Wissenschaft," 1885, Heft 4.

nature. Further, the metabolism is not raised after the ingestion of meat extract, so the chemical stimulus of flavors which start activity in the glands does not affect total metabolism. Again, the ingestion of water in the quantity contained in meat, while it may cause a rise in nitrogen in the urine followed by a fall—the rise being due to a rapid washing out of nitrogenous decomposition products—does not alter the total metabolism in any way.

Rubner determined the starvation metabolism and used this as a unit for the measurement of the absolute "requirement" of the organism. This "requirement" of energy may be met by the ingestion of an equivalent "maintenance diet" which covers the requirement. An "abundant diet" contains a larger amount of potential energy than the organism requires.

Rubner at first found that if the food ingested had a lower calorific value than the body's requirement, then the metabolism was not usually increased after the ingestion. This is illustrated in one of his earlier experiments[1] summarized below.

FOOD.	METABOLISM IN CALORIES.
Starvation	867
Bones, 40 grams	812
Meat, 720 grams	836
Meat, 760 grams	875

So if the food contains less than the energy requirement, the metabolism may not be increased in spite of activity of the glands and muscles of the intestinal tract.

To explain this Rubner[2] introduced his *compensation theory*. This assumed a certain reciprocity between the muscles and the glands. During starvation and medium temperature, a great part of the body's heat is produced in the muscles, and those cells ordinarily concerned in taking up food are quiet and produce little heat. On warming the outside air the amount of metabolism in the muscles decreases. The same thing may take place when gland cells and intestinal musculature are thrown into activity, the voluntary muscles are proportionally relieved.

[1] Rubner: "Zeitschrift für Biologie," 1883, Bd. xix, p. 349.

[2] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 8.

Quite a different picture is presented when an abundant diet is supplied to the dog. If proteid above the calorific requirement be ingested there is a very considerable rise in the heat production. This increase is greater in the case of proteid than with any other foodstuff. Rubner calls this action of abundant proteid food in raising the metabolism the *specific dynamic* action of proteid. This action is shown in the two experiments of Rubner cited on pages 122, 123. In the second experiment, the total metabolism during the starvation days is as follows:

First day	718.5 calories.
Second day	741.8 "
Third day	746.2 "
Fourth day	772.0 "

Rubner took the average of the last two days as representing the requirement in starvation, or 759.1 calories. After administering 2000 grams of meat containing 1962 calories, or the full starvation requirement and 153.7 per cent. besides, the heat production rose from 759.1 calories to 1046.34 and 1105.65 calories,—that is, it increased 42.2 and 45.6 per cent. Rubner recalculated the calories produced by the metabolism during the experiment on the assumption that the carbon from proteid was retained as glycogen and not as fat, and in this way estimated the increased metabolism after this ingestion of meat at 45.5 and 48.7 per cent. above the starvation minimum.

Combining the results of such experiments, Rubner[1] finds the following increasing specific dynamic effect of proteid as the quantity above the requirement becomes larger.

EXCESS ABOVE REQUIREMENT.	INCREASE IN HEAT PRODUCTION.
56 per cent.	19 per cent.
90 "	35 "
105 "	44 "
153 "	49 "

Here were increases in total metabolism comparable to those induced by considerable mechanical work. The body metabo-

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[1] "Rubner: "Gesetze des Energieverbrauchs," p. 90.

lized in largely increased measure without doing any external work.

A more rapid respiration alone betokened the increased oxidation and the effort of the body to rid itself of excess of heat through physical regulation. The temperature of the dogs scarcely changed, so perfect is the regulatory mechanism for the discharge of heat. Thus in one dog the temperature was 38.16° before the meal, 38.74° during the digestion, and 38.17° at the end of digestion.

Rubner differentiated between three stages of proteid metabolism. *First*, in the cases of undernutrition and of maintenance diet in which proteid enters into the circulation and spares an isodynamic quantity of the body substances; *second*, the state of abundant nutrition where the proteid raises the metabolism through its specific dynamic power; *third*, an intermediary stage where proteid may be added as tissue to the body without increasing the metabolism. This period of "pure deposit" of tissue may rapidly pass into the stage of deposit united with specific action causing increase in combustion. It will be apparent later that the first and third states of proteid nutrition can be achieved only at low or medium temperatures of environment.

An example of the stage of the deposit of proteid tissue without a rise in metabolism is given by Rubner[1] as follows:

	N to Body.	Calories per Kg.
Starvation	——	45.61
Starvation	——	43.26
Meat	+8.7	44.48
Meat	+4.7	46.16

This kind of growth of tissue without a corresponding rise in metabolism takes place in the normal adult only when the proteid ingested is below the heat value of the fasting metabolism. If, however, a larger quantity of proteid be ingested than the heat requirement of the body calls for, then the usual specific dynamic action occurs and also a continued "secondary" rise in total day-to-day metabolism, which increases as long as

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[1] Rubner: "Gesetze des Energieverbrauchs," p. 256.

proteid is deposited. When nitrogen equilibrium is established the heat production remains constant at a higher level.

Rubner[1] illustrates this important fact in the following experiment on a dog:

Calories in meat Ingested.	N to Body.	Carbon to Body.	Total Calories of Metabolism.
0	-1.31	...	310.61
0	-1.52	...	278.00
481.5	3.95	2.97	311.43
481.5	2.80	3.70	333.82
481.5	2.30	1.61	368.41
481.5	2.20	2.53	361.70
481.5	0.92	4.45	375.47
481.5	0.20	4.31	395.77
0	-3.70	...	357.20
0	-2.64	...	310.29

The constant deposit of proteid therefore continually raises the heat production in the organism until a point is reached when no more proteid is added to the body. This is the point of nitrogenous equilibrium, and is very quickly attained. It is evident that on a purely proteid diet no great addition of proteid tissue can ever take place in the adult on account of this *secondary dynamic action*, which causes a constantly increasing combustion, thereby bringing about nitrogenous equilibrium.

Rubner shows that the retention of fat from proteid in the body has nothing to do with this action. Proteid retention is much more readily brought about on a mixed diet containing large quantities of carbohydrates, as will be seen in a subsequent chapter.

Up to the present writing the influence of external temperature upon the course of proteid metabolism has not been discussed. Rubner has shown that this is a factor of profound significance. It has already been demonstrated how, through *chemical regulation*, the basal requirement of the body is reflexly increased by increasing cold in the environment. Rubner[2] compared the starving metabolism of a dog at different temperatures with that of the same dog when 100, 200, and 320 grams of meat were ingested. The results are presented as

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[1] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 246.

[2] Rubner: *Ibid.*, p. 109.

follows in terms of calories produced per kilogram of body weight:

INFLUENCE OF EXTERNAL TEMPERATURE ON METABOLISM AFTER PROTEID INGESTION.

Temperature.	Starvation.	100 Gm. Meat or 24 Cal. per Kg.	200 Gm. Meat or 48 Cal. per Kg.	320 Gm. Meat or 81 Cal. per Kg.
7°..........	86.4	....	77.7	87.9
15°..........	63.0	....	....	86.6
20°..........	55.9	55.9	57.9	76.3
25°..........	54.2	55.5	64.9	....
30°..........	56.2	55.6	63.4	83.0

One hundred grams of meat did not change the metabolism at 20°, 25°, or 30°; 200 grams of meat had no effect at 20° or at 7°, but at 25° and at 30° there was an increase although the food contained fewer calories than the requirement. With 320 grams of meat there was a great increase above the starvation requirement, except at 7°, where it is a maintenance diet and the metabolism remains unchanged. In other words at a temperature of 30° the specific dynamic action of this amount of proteid is capable of increasing the heat production above that of starvation by about 53 per cent., while at 7° there is no change whatever. It is also evident that at a high temperature even a small quantity of proteid such as 200 grams meat causes a considerable rise of metabolism.

Rubner gives the metabolism in terms of calories per kilogram after the ingestion of 550 grams of meat or 173.8 calories per kilogram of body weight in a dog, as follows:

Temperature.	Starvation.	550 Grams Meat.	Increase.
4.2°....	128.1	133.5	4.2 per cent.
14.5°....	100.9	110.9	9.9 "
22.1°....	70.7	101.0	42.9 "
30.7°....	62.0	117.2	89.0 "

These experiments make evident the extraordinary influence of variations in the surrounding temperature on the metabolism when the same quantity of meat is fed. The influence of temperature must therefore be continually kept in mind as a most

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important factor of the amount of the metabolism. Many experiments reported as having been done at the "room temperature" have an indefinite value.

An additional point of interest is that in certain cases the number of calories remains constant throughout the experiment, notwithstanding a variation in the temperature. This is shown on p. 129, where the dog was given 320 grams of meat. The amount of the metabolism scarcely varied with the temperature. The chemical regulation, or the increased heat production brought about by a reduction of the surrounding temperature, is not evident in this case. Here the fuel value of the food was equal to the requirement of the body even at a temperature of 7°.

From the general results of these experiments Rubner[1] deduces two important laws which govern metabolism as influenced by temperature. Their significance will be better appreciated in the analysis of the subject in the following chapter.

"*The first law is that within limits normally compatible with life, warm-blooded animals are capable of adapting themselves to change in external temperature through a reflex increase or decrease of the activity of their heat-producing apparatus. For every state of body substance and for every temperature of the environment there is a definite amount of heat loss to which the organism—with the aid of its heat-regulating apparatus—tends to approach. This may be called the minimal heat requirement.* There is no law enforced with greater severity or fatality. The starving man who lives on his own substance cannot remove himself from its influence. Inexorable until the last hour of life it demands fulfilment. . . . . It kills the starving child in days, while it allows the starving adult weeks."

"The second law concerning the relation of external temperature to the organism is: *The physical regulation can never enter as a factor unless the conditions of the first law are fully satisfied*, i. e., *until the heat production equals the requirement of the organism. If, however, the heat production be greater than corresponds to the minimal requirement for that temperature, then*

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[1] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 160.

the heat production within certain limits remains independent of the temperature. Under these circumstances the heat production does not decrease on raising the external temperature, and only increases when through increasing cold the former heat production no longer covers the minimal requirement of the organism for heat."

This second law explains why in certain cases after food ingestion the carbon dioxid excretion may remain constant with changing temperatures. Its action is seen in the dog mentioned on page 129, after he had eaten 320 grams of meat at various temperatures. The increase in body metabolism due to the stimulus of cold (chemical regulation) is not necessary, since heat in excess of the requirement is already available. All that is needed is the arrangement of avenues of escape for the excess of heat produced from the food ingested (physical regulation). This physical regulation is brought about by the evaporation of water and by the distribution of the blood.

How the increased evaporation of water enters as a refrigerating factor is beautifully shown in the experiment on the dog (p. 129) which fasted and then received 100, 200, and 320 grams of meat at various temperatures. The distribution of the loss of heat by radiation and conduction and by the evaporation of water was as follows:

DISTRIBUTION OF HEAT LOSS FROM A DOG AFTER MEAT INGESTION.

Temperature.	Hunger.		100 Grams Meat.		200 Grams Meat.		320 Grams Meat.	
	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.
7°	78.5	7.9	...	...	67.1	10.6	78.5	9.4
15°	55.3	7.7	...	...	46.7	11.2	76.2	10.4
20°	45.3	10.6	46.7	9.2	49.5	15.4	...	...
25°	41.0	13.2	...	...	...	...	...	...
30°	33.2	23.0	34.1	21.5	27.8	35.6	34.5	48.5

It is evident from the above that the greater part of the loss of heat at a low temperature was by radiation and conduction, but at a high temperature (30°) the loss by the evaporation of water was largely increased. The increased heat production, on account of the specific dynamic action of the proteid, was lost through the increased evaporation of water.

Much meat on a hot day would therefore seem contraindicated.

While the chemical regulation protects the body from an abnormal fall in temperature, the physical regulation prevents an abnormal rise in temperature. The organism may be at times under the influence of one means of regulation, at times of the other, and without being conscious of any difference.

Cold-blooded animals have no chemical regulation, and their temperature falls with that of their surroundings.

The following chapter will more fully discuss the cause of the specific dynamic action of the foodstuffs.

CHAPTER VI.

THE SPECIFIC DYNAMIC ACTION OF THE FOODSTUFFS.

A study of the specific dynamic action of proteid in its relation to temperature changes gave Rubner[1] new points of view. He saw (experiment on p. 129) that by chemical regulation the metabolism in a fasting dog was increased from 54 to 86 calories per kilogram, an increment of 32. And he likewise observed after the ingestion of 320 grams of meat that the heat produced at a room temperature of 30° rose from 56 in starvation to 83, a difference of 27 calories. The source of the increase through chemical regulation is known to be chiefly in the muscles. The increase brought about by proteid ingestion had been shown by Rubner to be due not to any such thing as intestinal activity (Darmarbeit) but rather to some specific heat-raising effect of proteid metabolism itself. It was apparent that these two sources of increased heat might enter into a reciprocal arrangement because on cooling the atmosphere in which the dog lived to 7° C., the metabolism, after the ingestion of 320 grams of meat, remained at 87.9 calories in contrast with 83.0 on feeding at 30°. Here the calories of the specific dynamic action were used in replacement of the calories through the chemical regulation. This illustrates Rubner's modified idea of his *compensation theory*, or a reciprocity between heat produced in the muscles by chemical regulation and the extra heat production brought about through the ingestion of food.

Since the extra heat production after food ingestion could be utilized instead of heat from chemical regulation, Rubner perceived that the true increase through specific dynamic action could be measured only at the temperature of 33°, where there was no reflex increase in metabolism through chemical regulation.

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[1] Rubner: "Energiegesetze," p. 145.

It was especially important to make experiments regarding the action of foodstuffs at a temperature of 33°, for that is the temperature with which man surrounds his skin. By means of clothes and artificial heating man constantly tries to remove himself from the influence of chemical regulation. His daily life is practically under the influence of a tropical climate. His metabolism is unchanged from the normal when he is immersed in a bath at 33°.[1]

Rubner therefore planned an experiment in which a dog was kept at a temperature of 33°. At times the animal fasted in order that the basal requirement could be determined, and during other definite periods, meat, fat, and carbohydrates, either alone or combined, were ingested, and the increased metabolism due to the varying dietaries was noticed. The experiment extended over a period of forty-six days.

A summary of the results obtained is shown in the following table and is graphically illustrated by the accompanying figure 8, which has been taken from Rubner.[2]

TABLE INDICATING THE SPECIFIC DYNAMIC ACTION OF DIFFERENT FOODSTUFFS AT 33°.

VALUES IN CALORIES PER KILOGRAM BODY WEIGHT.

DIET.*	HUNGER REQUIREMENT.	FOOD INGESTED.	PROTEID INGESTED.	METABOLISM.	INCREASE ABOVE HUNGER IN PER CENT.
100 per cent. fat	54.0	53.4	.. .	60.9	12.7
66 per cent. meat ..	53.5	37.7	32.3	62.1	16.0
10 per cent. meat 90 per cent. fat..	53.4	55.5	5.1	60.6	13.4
20 per cent. meat 80 per cent. fat..	52.5	59.3	10.5	63.6	21.5
100 per cent. meat ..	52.0	63.0	57.1	73.8	41.9
Meat, fat, sugar.....	51.0	59.8	8.8	55.6	9.0
100 per cent. meat ..	51.0	60.3	56.3	67.3	31.9
Meat, fat, starch....	50.0	48.0	8.1	53.0	4.0
87 per cent. sugar..	50.0	43.6	.. .	52.5	5.0
66 per cent. meat ..	50.0	34.5	31.6	60.4	20.8

* Percentages are in terms of the starvation requirement and are approximate only.

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[1] Rubner: "Archiv für Hygiene," 1903, Bd. xlvi, p. 390.

[2] Rubner: "Energiegesetze," p. 324.

It is clearly evident that meat ingestion raises the metabolism most, fat next, and sugar least of all the foodstuffs. The ingestion of the starvation requirement for energy in the form of fat raises the metabolism 12.7 per cent. During the two periods when approximately 100 per cent. of the basal requirement was ingested as meat there was an *average increase* in the metabolism of 36.7 per cent.

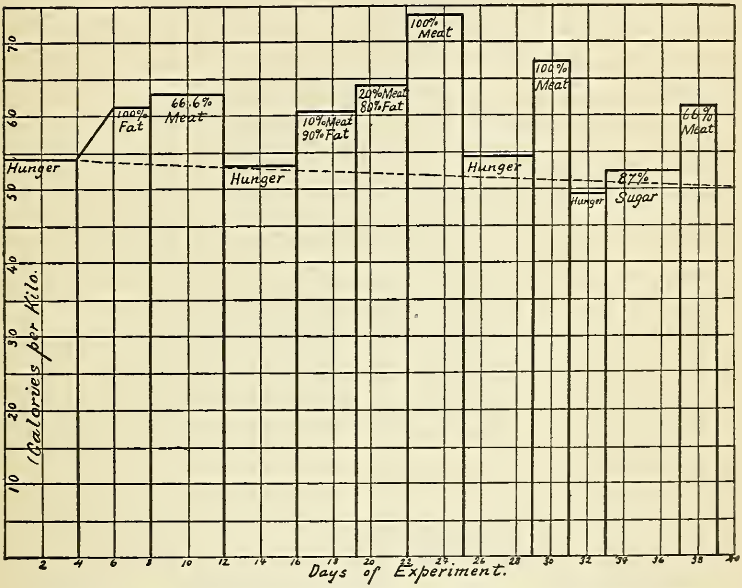

Fig. 8.—Rubner's chart indicating the specific dynamic action of different foodstuffs ingested at a room temperature of 33°. The dotted line indicates the height of the fasting metabolism.

More detailed examination, however, reveals the fact that the exact quantity of meat ingested contained 119.6 per cent. of the basal requirement of calories, of which 110.1 were contained in meat proteid and the balance in fat present in the meat. If under the influence of the ingestion of 119.6 per cent. of the basal requirement the metabolism rose 36.7 per cent., then the increase due to the ingestion of 100 per cent. would have been 30.74 per cent. But this meat containing 100 per cent of the basal requirement in reality consisted of meat proteid containing 92.06 per cent. of the energy and of fat containing the remaining 7.94 per cent. Since the ingestion of fat sufficient to provide 100 per cent. of the basal requirement for energy raises metabolism 12.7 per cent., then fat sufficient to provide 7.94 per cent. of the basal requirement must increase metabolism 7.94 × 0.127 or 1.01 per cent.

Deducting this 1.01 per cent. which is due to the specific dynamic action of the fat ingestion from the total increase of 30.74 per cent. it is found that 29.73 per cent. increase is due to the 92.06 per cent. of pure meat proteid ingested.

If 92.06 per cent. of meat proteid raises the metabolism 29.73 per cent. then 100 per cent. of such proteid will increase it by 32.28 per cent. Using the same procedure in computing the heat-raising power of two-thirds the basal requirement of energy for the dog, ingested in the form of meat, it was calculated that if 100 per cent. of the requirement had been the quantity supplied the increase in the metabolism would have been 29.60 per cent. Rubner therefore found that—

I. After ingesting meat in excess of the starvation metabolism, the specific dynamic action caused a heat increase of 32.28 per cent.

II. After ingestion of a smaller quantity the specific dynamic action similarly measured was 29.60 per cent.

The average of these, or 30.94 per cent., represents the specific dynamic action of proteid or the increased heat production after the ingestion of meat containing 100 per cent. of the energy requirement, when the animal is outside of the influence of the chemical regulation.

In another case, after the ingestion of meat in large excess, Rubner finds the increase due to the specific dynamic action to be 32.2 per cent. The action of gelatin is similar, the increase in metabolism being 28.0 per cent. for every 100 calories in the gelatin ingested.

Again Rubner[1] has determined the amount of the metabol-

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[1] Rubner: "Energiegesetze," p. 370.

ism of a fasting dog and that of the same dog made diabetic with phlorhizin (see p. 237). Under the latter circumstances the proteid metabolism is greatly increased. He found that for every 100 calories increase in body proteid broken down there was an increased heat production of 31.9 calories. Here was a rise in heat production not due to proteid ingestion and therefore not due to intestinal work, but due to the mere fact of increased proteid metabolism in starvation. The specific dynamic action of proteid then may thus be tabulated:

INCREASED HEAT PRODUCTION FOR EVERY 100 CALORIES INGESTED OR METABOLIZED.

Meat proteid	30.9
Gelatin	28.0
Body proteid (phlorhizin diabetes)	31.9

Considering the conditions of experimentation these figures are wonderfully alike, and, if confirmed, will rank with the great achievements in the study of metabolism.

Regarding cane sugar, the experiment shows that after its ingestion to the extent of providing 86.41 per cent of the starvation requirement for energy, the metabolism increased only 5 per cent. It may be calculated that if 100 per cent. of the basal requirement had been given the increase would have been 5.8 per cent.

Summarizing, it is evident that if the same quantity of energy be contained in the ingested food as the body requires in starvation at a temperature of 33° C., there will be the following increases in heat production:

Proteid	30.9 per cent.
Fat	12.7 per cent.
Cane sugar	5.8 per cent.

The basal requirement in starvation at the temperature of 33° cannot therefore maintain the body in calorific equilibrium. Rubner, however, calculates the following as the minima of ingestion for the three foodstuffs, when the hunger minimum is 100:

Hunger minimum	100
Proteid “	140.2
Fat “	114.5
Cane sugar minimum	106.4

In other words, if 100 calories be the starvation requirement, 140 calories must be supplied if calorific equilibrium is to be maintained by the ingestion of proteid alone; whereas in the case of sugar, 106.4 calories are all that are required to prevent the loss of energy content from the body's material. That these results are not limited in their application is shown by Rubner's[1] experiment on a man who was given 120 per cent. of the starvation requirement of energy first in the form of sugar and then of meat. The metabolism was as follows:

Starvation	2042 calories in 24 hours.
Sugar alone	2087 “ “ “ “
Meat alone	2566 “ “ “ “

As neither man nor dog ever lives on meat alone except under forced feeding, the results are not usually so pronounced as in the above case. Average dietaries, according to Rubner[2] show the following distribution of percentage of calories:

PERCENTAGE OF CALORIES IN DIFFERENT DIETS.

	PROTEID.	FAT.	CARBOHYDRATES.
I.—Well-to-do individual	19.2	29.8	51.0
II.—Workman	16.7	16.3	66.9
III.—Extreme cases (poverty, etc.)	8.3	38.7	52.8

It is possible to calculate the specific dynamic effect of such diets by multiplying the foodstuffs by their specific dynamic factor,—for example, 100 per cent. of proteid $= 30.9$ per cent. increase; 1 per cent. $= 0.309$ per cent. increase, and therefore 19.2 per cent. proteid in the food must cause an increase of $0.309 \times 19.2 = 5.93$ per cent. in the metabolism due to the ingestion of proteid in Diet I.

Calculating the diets as above, the following figures are obtained:

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[1] Rubner: "Energiegesetze," p. 410.

[2] Rubner: *Ibid.*, p. 415.

I. Proteid..............19.2 × 0.309 = 5.93
Fat.................29.8 × 0.127 = 3.77
Carbohydrate........51.0 × 0.058 = 2.96
+ 12.66 per cent.

II. Proteid.............16.7 × 0.309 = 5.15
Fat.................16.3 × 0.127 = 2.06
Carbohydrate........66.9 × 0.058 = 3.88
+ 11.09 per cent.

III. Proteid............. 8.3 × 0.309 = 2.56
Fat.................38.7 × 0.127 = 4.91
Carbohydrate........52.8 × 0.058 = 3.06
+ 10.53 per cent.

Thus, if the starvation requirement for energy be ingested the increase in metabolism would be:

Diet I	12.66 per cent.
" II	11.09 "
" III	10.52 "

and from this it may be calculated that calorific equilibrium would be reached by ingesting the following increases above the starvation requirement:

Diet I	14.4 per cent.
" II	12.4 "
" III	11.1 "

On an average mixed diet the ingestion minimum is therefore between 11.1 *and* 14.4 *per cent. above the starvation requirement. This would be the maintenance requirement.* (Rubner.)

Should the fasting metabolism of a man be 2400 calories, the ingestion of food would act as follows:

	Diet I. (19.2% proteid)	Diet III. (8.3% proteid)
After ingestion of starvation requirement of energy	2703	2652
After ingestion of maintenance minimum	2745	2666

That mixtures of the foodstuffs do act nearly after this fashion Rubner has proved.

On account of the great specific dynamic action of proteid, Rubner would restrict its use in fever and substitute carbohydrates as the source of energy.

During the heated term of midsummer, decreased proteid ingestion will materially improve the personal comfort by decreasing the heat production and the consequent necessity for sweat production (p. 183).

As to the cause of the specific dynamic action, Rubner offers this explanation: The cells of an organism require a fixed quantity of potential energy which must be furnished to them in metabolizable compounds. This quantity is the same for all temperatures and free heat cannot be employed for this purpose. The value of the foodstuffs depends upon the potential energy they can give to the cells. If cane sugar is ingested, for example, 3.1 per cent. of its energy is dissipated as heat when it is inverted into levulose and dextrose. This heat cannot be used for the life processes in the cells. When proteid breaks up in metabolism, large quantities of sugar are produced. According to Rubner, this earlier metabolism of proteid yields heat, but not energy for the cells. He thinks that the proteid sugar and possibly other cleavage compounds may in this case be the true source of power for the living mechanism. The extra heat of the earlier process which is wasted when the environment has a temperature of 33°, may however be used as a substitute in the place of the heat, which may be required by chemical regulation. Here heat and not potential energy is required. Bearing these considerations in mind, foodstuffs are replaceable in accordance with their specific respective equivalents.

The theory may be schematically indicated as follows:

STARVATION REQUIREMENT OF POTENTIAL ENERGY BY CELLS = 100 CALORIES.

140 Calories in Proteid Meat Ingested.

40 Calories = free heat liberated in early cleavage, available in replacement of heat of chemical regulation.

100 Calories = Potential energy from proteid available for cell life.

From this it may be calculated that when proteid is metabolized 71.4 per cent. of its energy content is available for cell life, while 28.6 per cent. is liberated as free heat. It has been already shown that 52.5 per cent. of the energy contained in meat proteid may be liberated in dextrose in the organism (see p. 113), and this may be directly used by the cells. The balance of the 71.4 per cent. of the directly available energy (=a residual 19 per cent.) is furnished by unknown compounds. As regards the source of the free heat the writer believes that it may be largely derived from the denitrogenization of the amino cleavage products of proteid metabolism. If one considers the case of alanin, which is known to be converted into lactic acid and ammonia by hydrolysis in the organism (p. 232), it is found that one gram of alanin with a calorific value of 4372, is almost exactly converted in one gram of lactic acid with a calorific value of 3661[1] (Berthelot). Here occurs a loss of heat equal to 16 per cent. The energy of lactic acid may be used by the cells either directly or through the conversion into dextrose (see p. 247), but it is quite conceivable that the heat liberated in its production from alanin cannot be so used. This elementary example would serve to explain the principle of the specific dynamic action of proteid in the light of most recent knowledge. It may also be possible that such a cleavage as that when leucin is converted into acetone and alanin (p. 232) may liberate free heat of similar physiological value to the above.

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[1] Dr. F. G. Benedict very kindly sends me information from which a calorific value of 3608 may be calculated for 1 gram of lactic acid present in the commercial product.

CHAPTER VII.

THE INFLUENCE OF THE INGESTION OF FAT AND CARBOHYDRATE.

In a previous chapter it was shown that the amount of fat in the fasting organism materially affected the amount of proteid burned. Where there was much fat present little proteid was consumed; where there was little fat, much proteid burned; and where there was no fat, proteid alone yielded the energy necessary for life.

The ingestion of fat alone will not prevent the death of the organism because there is a continual loss of tissue proteid from the body, which finally weakens some vital organ to such an extent that death takes place.

In a fasting animal which still contained fat, Voit[1] found that the ingestion of 100, 200, and 300 grams of fat scarcely influenced the proteid metabolism. The latter was slightly increased, if anything. Voit's table is as follows:

Fat.	Urea.
0	11.9
0	12.0
100	12.0
200	12.4
300	12.0
0	11.9
0	11.3

To another dog which in starvation burned 96 grams of fat, 100 grams were given with the result that he then burned 97 grams. The conditions of the metabolism in both cases were therefore identical. The fat ingested simply burned instead of the body's fat, but the total amount of proteid and fat burned remained the same. Only on giving large quantities of fat were both fat and proteid metabolism increased.

One reason why the ingestion of fat up to the requirement does not alter the metabolism may be found in the observation

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[1] Voit: "Physiologie des Stoffwechsels und der Ernährung," 1881, p. 128.

of Schulz[1] that in starvation there is an increase in the quantity of fat in the blood, and of Rosenfeld[2] that the amount of fat in the liver increases. He finds that a fasting liver contains 10 per cent. of fat. If carbohydrates or proteid (which yields carbohydrate in metabolism) be ingested, the fat content falls to 6.2 per cent. If fat be given to a fasting dog, the liver may contain 25 per cent. of fat; but if carbohydrates are ingested at the same time, the liver does not retain the fat, which must be deposited elsewhere. Thus, in the liver there is an antagonism between glycogen deposit, which follows carbohydrate ingestion, and fat deposition.

Meischer found fat globules in the muscle cells of salmon after their five to fifteen months' fast in fresh water, during which time they had laid their eggs. It is undoubted that the deposits of fat in the adipose tissue of these fish are drawn on in starvation, and that the blood then carries to the hungry cells all the fat they require for their continued function. It seems that the fat supply to the cells is regulated by the quantity of other foods available, and that even in starvation there is at first ample fat to meet the requirement of the organism. These are important principles which will be further discussed when the subject of fatty infiltration is considered. (See Chapter on Diabetes).

As explained in Chapter VI, the small increase in metabolism after the ingestion of fat above the requirement has led Rubner[3] to determine accurately its specific dynamic action. The metabolism does not rise so greatly after the ingestion of fat as it does on a proteid diet. If the hunger minimum of calories at 33° be 100, then 114.5 calories must be ingested in fat if a maintenance diet is to be given. This energy requirement is 140.2 in the case of proteid diet. Proteid therefore causes a much higher heat production than does fat. The influence of external temperature on the heat production after ingesting fat above

[1] Schulz: "Pflüger's Archiv," 1896, Bd. lxv, p. 299.

[2] Rosenfeld: "Ergebnisse der Physiologie," 1903, Bd. ii, I, p. 86.

[3] Rubner: "Energiegesetze," 1902, p. 353.

the requirement is similar to that after meat ingestion, only not so pronounced. Rubner[1] gives the following table, showing the effect of the ingestion of 171.3 calories in fat per kilogram of dog:

SPECIFIC DYNAMIC ACTION OF FAT.

171.3 calories in fat per kg. dog were ingested.

Temperature.	Calories per Kilo.		Increase.
	Starvation.	After Fat Ingestion.	
2.7°	152.1	155.5	+ 2.2 per cent.
15.5°	83.1	93.4	+12.4 "
31.0°	64.5	79.9	+23.9 "

At 2.7° the excess ingested above the requirement amounted to 12.6 per cent., and the increase in heat production was 2.2 per cent.

At 31° the excess of food calories above the requirement was 165 per cent. and the increase in heat production was 23.9 per cent. In this instance 100 per cent. of the requirement may be calculated to raise the metabolism 14.4 per cent. at a temperature of 31°. This represents the specific dynamic effect of fat on the metabolism. As in the cases of the other foodstuffs, this action is to be explained by a production of heat in early cleavage processes which is not directly available for the cells of the organism.

It has already been demonstrated that less proteid is burned in starvation when the body is fat than when it is lean. It would therefore seem that if proteid and fat were ingested together, a similar reduction in the amount of the proteid requirement would be effected (Voit).

It has been shown in a previous chapter that nitrogenous equilibrium can be maintained in a dog only after the ingestion of three and a half times the quantity of proteid destroyed in starvation (see p. 100).

E. Voit and Korkunoff,[2] continuing these experiments, find that if fat and meat be ingested together, the quantity of the former necessary to establish nitrogenous equilibrium is reduced to between 1.6 to 2.1 times the starvation minimum. Much

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[1] Rubner: "Energiegesetze," 1902, p. 119.

[2] Voit and Korkunoff: "Zeitschrift für Biologie," 1895, Bd. xxxii, p. 117.

less proteid food is therefore required to maintain the body's proteid when it is ingested with fat than when it is given alone. In consequence of this, proteid is more readily added to the body when fat is ingested with it, as is seen in the following experiment of Rubner[1] on a man.

INFLUENCE OF FAT INGESTION ON NITROGEN RETENTION.

Food.			N. Metabolism.	
N.	Fat.	Carbohydrates.	N in Excreta.	N to Body.
23.6	99.	260	26.36	—3.64
23.5	195.	226	21.55	+1.81
23.0	214.	221	18.5	+4.13
23.4	350.	234	17.6	+5.75

With increasing quantities of fat there is an increasing addition of proteid to the body.

It has already been shown that proteid ingested alone in large quantity establishes nitrogen equilibrium at a higher level, constantly raising the amount of heat produced until nitrogenous equilibrium is reached (the secondary dynamic rise, p. 128).

The same destruction of the easily burned proteid takes place when it is given with fat, as was shown by Voit[2] in the following experiment on a dog:

THE "SECONDARY RISE" IN PROTEID METABOLISM ON A MEAT-FAT DIET.

(Weights in grams.)

Food.			
Meat.	Fat.	Urea.	Flesh to Body.
1800	0	127.9	26
1800	0	127.6	26
1800	250	117.9	162
1800	250	113.5	171
1800	250	120.7	
1800	250	115.7	164
1800	250	119.7	
1800	250	127.5	11
1800	250	130.0	

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[1] Rubner: Von Leyden's "Handbuch der Ernährungstherapie," 1903, Bd. i, p. 43.

[2] Voit: Hermann's Handbuch, "Physiologie des Stoffwechsels," 1881, p. 131.

A prolonged deposition of proteid in the normal adult, even when fat is given with it, is demonstrably impossible.

The question arises, does the ingestion of large quantities of fat also cause an increase in the metabolism until fat combustion is balanced by its ingestion?

Rubner[1] has shown that this is not the case. He cites the record of the following long respiration experiment on a dog which was given 80 grams of meat and 30 grams of fat daily:

ABSENCE OF THE "SECONDARY DYNAMIC RISE" IN FAT METABOLISM ON A MEAT-FAT DIET.

(Fat being given in excess of the requirement.)

Calories of Metabolism.		
Proteid	Fat.	Total.
97.2	173.0	270.0
83.0	178.0	261.1
89.3	173.5	262.7
85.6	163.2	248.9
87.8	169.0	256.8
83.0	159.6	242.6
74.4	171.7	246.2
78.0	178.4	256.3
80.0	179.6	259.7

The diet was 58.7 per cent. above the starvation requirement. It contained 354 calories of which 21.5 per cent. were in proteid. The mean heat production during the period of ingestion of food was 256.0 calories, and in the following starvation days 223.2 calories, showing an increase in metabolism of 11.2 per cent. caused by an excess in food of 58.7 per cent. During the later days the animal was in nitrogenous equilibrium. Notwithstanding an excess of fat in the diet, and a continued deposit of fat in the body, there was no increase in the metabolism during the time of experimentation. The secondary dynamic action noted by Rubner as regards proteid does not therefore take place as regards fat. The storage of fat in the body is consequently a matter of comparative ease.

Rubner[2] has compared the metabolism of a boy who was obese with that of his brother who was a year older, but thin.

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[1] Rubner: "Energiegesetze," 1902, p. 251.

[2] Rubner: "Beiträge zur Ernährung im Knabenalter," 1902.

They were the children of parents of limited means and would not naturally be overfed. The interesting point of the experiment was whether obesity was due to a reduced metabolism with the consequent deposition of fat. Each boy was given a maintenance diet, or one which balanced his metabolism, without adding or subtracting from his body substance. The general results are as follows:

	FAT BOY.	THIN BOY.
Age in years	10	11
Weight in kilograms	41	26
Total calories of metabolism	1786.1	1352.1
Calories per kilogram	43.6	52.0
Calories per sq. m. surface	1321.	1290.

The comparison shows that the fat brother had a larger total metabolism than the thin one, but the fat boy also had the larger surface. Per square meter of surface the metabolism was the same. The gradual increase in the area of the body caused by filling out the fat cells may therefore increase combustion, but this is not due to the specific action of the fat on metabolism as in the case of the secondary dynamic rise after proteid ingestion, but rather to the increase in the size of the body. Carbohydrates, which in excess are converted into fat, must behave in the same way.

It will be noticed that in the experiment where 80 grams of meat and 30 grams of fat were daily ingested, although the proteid metabolism gradually fell, the fat metabolism gradually rose, and in isodynamic relation to the fall in proteid. Allowing for the difference in specific dynamic action proteid and fat replace each other in metabolism in isodynamic quantities.

Up to the present the discussion of metabolism has been confined to the combustion of proteid and fat in starvation and after their ingestion. There is, however, another great class of foodstuffs which in man play a predominant part in nutrition,—the carbohydrates.

Starch, milk sugar and cane sugar are all converted into monosaccharids in the intestinal tract, and dextrose, galactose and levulose, formed from them, have similar physiological value in the cells. All three are glycogen formers, and thus galactose and levulose may be partly converted into dextrose through the glycogen stage.

It has already been noted that starvation greatly reduces the quantity of glycogen in the animal body. If under these circumstances dextrose, levulose, or galactose be ingested in considerable quantity and the animal be killed eight hours after the experiment, large quantities of glycogen are found stored in the liver and muscles. The amount in the liver may be as high as forty per cent. of the dry solids of that organ.[1] The quantity found is much more than could have originated from the proteid metabolism of the time. There is therefore no doubt that these sugars are directly converted into glycogen through dehydration.

The quantity of glycogen present in a living animal cannot be accurately estimated. Schöndorf[2] gave seven dogs rich carbohydrate diets for several days and found that the quantity of glycogen present in their bodies varied between 7.59 and 37.87 grams per kilogram.

The distribution of this glycogen in 100 grams of the fresh tissue varied as follows:

	MAXIMUM.	MINIMUM.
Liver	18.69	7.3
Muscle	3.72	0.72
Heart	1.32	0.104
Bone	1.90	0.197
Intestines	1.84	0.026
Skin	1.68	0.09
Brain	0.29	0.047
Blood	0.0066	0.0016

The traditional distribution of glycogen, one-half to the liver and one-half to the rest of the body, Schöndorf shows to be incorrect. For 100 grams of liver glycogen there occurred in the rest of the body the following amounts:

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[1] Voit: "Zeitschrift für Biologie," 1891, Bd. xxviii, p. 245.

[2] Schöndorf: "Pflüger's Archiv," 1903, Bd. xcix, p. 191.

Dog	I	398. grams.
"	II	279. "
"	III	87. "
"	IV	76. "
"	V	159. "
"	VI	355. "
"	VII	105. "

It is an interesting observation of Külz[1] and of Jensen[2] that an active organ like the heart maintains its normal glycogen content even after fifteen days of starvation.

In the various discussions on the subject of glycogen it has been shown that in starvation, and after proteid and sugar ingestion, there is glycogen present in the body,—a constant supply always ready for emergencies, which can be reduced through exercise but which is only to be completely removed by tetanic convulsions (p. 71).

The writer has here avoided the discussion of a production of sugar from fat. To his mind the evidence is negative, as will be demonstrated in the Chapter on Diabetes.

If carbohydrates be ingested alone immediately after starvation the proteid metabolism may fall below the starvation amount. This appears in the experiments of Voit[3] who gave a fasting dog 500 grams and noticed a fall in proteid metabolism from 181 to 170 grams.

Rubner[4] was able to reduce the nitrogen in the urine of a fasting man from 11.9 to 6.3 grams, or nearly one-half, by causing the subject to ingest carbohydrates alone.

This higher proteid-sparing property gives to dogs fed on carbohydrates alone a longer lease of life than those fed on fat alone, although the ultimate outcome is the same.

The effect of feeding with easily absorbable sugar in excess is shown in the following experiment of Rubner[5] on a dog:

[1] Külz: "Festschrift zu Ludwig," 1891, p. 109.

[2] Jensen: "Zeitschrift für physiologische Chemie," 1902, Bd. xxxv, p. 525.

[3] Voit: Hermann's Handbuch, "Stoffwechsel," 1881, p. 140.

[4] Rubner: von Leyden's Handbuch, 1903, vol. i, p. 44.

[5] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 341.

INFLUENCE OF CANE SUGAR ON THE METABOLISM OF A DOG.

Food.	N in Excreta in Grams.	C Retained from Carbohydrates in Grams.	Cal. from Proteid.	Cal. from Fat or Carbohydrates.	Calories, Total.
Starvation	1.92	....	48.0	203.4	251.4
Starvation	1.82	....	45.5	208.0	253.0
85 grams cane sugar	0.91	10.18	22.7	224.4	247.1
110 " " "	0.72	17.81	18.0	245.9	263.9
110 " " "	0.56	17.61	14.0	247.7	261.7
120 " " "	0.53	6.70	13.2	....	....
Starvation	0.69	....	17.2	208.8	226.0

The proteid metabolism may thus be reduced to one-third the fasting value, a result also obtained by Landergren[1] and by Folin[2] in man.

The quantity of sugar utilized by Rubner's dog was 35.7 to 80.6 per cent. above the starvation requirement for energy (the cane sugar eliminated in the urine was deducted from that ingested, in order to determine the quantity utilized). The experiment was done at 33°, and the specific dynamic action of the cane sugar may be calculated as raising the metabolism 5.36 per cent. on an average.

This experiment illustrates the ready retention of carbohydrate carbon in the body. It is well known that such carbon may be stored in the body as glycogen, but its retention often exceeds the animal's ability to hold glycogen.

Voit, when he wrote his "Physiologie des Gesammt Stoffwechsels und der Ernährung," in 1881, was unable to give definite proofs of the conversion of carbohydrate into fat in the organism, although such conversion was popularly believed to take place.

Definite proof of the conversion of carbohydrates into fat was afforded by Meissl and Strohmer[3] who gave a pig, weighing 140 kilos, two kilograms of rice daily, and collected the carbon

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[1] Landergren: "Skan. Archiv für Physiologie," 1903, Bd. xiv, p. 112.

[2] Folin: "American Journal of Physiology," 1905, vol. xiii, p. 45.

[3] Meissl and Strohmer: "Sitzungsberichte der k. Acad. d. Wissenschaften," 1883, Bd. lxxxviii, III Abtheilung.

and nitrogen of the excreta by means of a Pettenkofer-Voit apparatus. The results were as follows:

	CARBON.	NITROGEN.
Ingested in food	765.37	18.67
Excreted	476.15	12.59
Balance retained in the body	289.22	6.08

The nitrogen retained represented 38 grams of proteid containing 20.1 grams of carbon; 269.12 grams of retained carbon were therefore available for glycogen or fat construction. Since the amount of carbon retained exceeded the possible glycogen formation, fat must therefore have been added to the body. Had all the carbon retained been converted into fat it would represent a production of 343.9 grams of fat. This indicates a possible conversion of 21.5 per cent. of the starch ingested into fat.

Similar experiments were made with geese by E. Voit and C. Lehmann.[1] The geese were starved four and a half days and were then fed with rice.

One of these respiration experiments which lasted thirteen days has recently been published[2] and is as follows:

	NITROGEN.	CARBON.
In the 2609 grams of rice	41.47	1159.7
In the excreta—		
Urine and feces	45.39	134.8
Respiration	....	657.8
Total	45.39	792.4
Change in the body	—3.92	+367.3

At the commencement of the experiment the animal weighed 4 kilograms. There was no proteid retention, but 31 per cent. of the carbon ingested was not egested. The proteid metabolism could not nearly yield enough carbon to account for that retained. As the rice contained but 0.51 per cent. of ether extract the retained carbon could not have been administered in the form of fat. If 367.3 grams of carbon had been retained

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[1] Voit: "Sitzungsberichte der kgl. bayr. Acad. d. Wissenschaft," 1885, p. 288.

[2] Lehmann and E. Voit: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 644.

in the form of glycogen this would have aggregated 851 grams, or twenty per cent. of the whole goose. This is a manifest impossibility since E. Voit[1] found only 2.2 per cent. of glycogen in a goose which had been largely fed on rice. Since the carbon retained could not have been stored as glycogen, the only alternative remaining is to assume its retention as fat.

Rubner at the same time showed the same principles to be true in the case of the dog.

It is evident, then, that pigs, geese, and dogs can convert carbohydrates into fat. The fattening of cattle may be similarly accomplished. Weinland[2] has expressed from living ascaris ferments which convert glycogen into dextrose and then into valerianic and possibly caproic acids,—0.8 gram of dextrose yields 0.3 gram of valerianic acid.

This is suggestive of a widespread biological capability.

When carbohydrates are converted into fat in the organism the respiratory quotient ($\frac{\text{Volume CO}_2}{\text{Volume O}_2}$ see p. 27), may rise very considerably above unity. This is for the reason that an oxygen rich substance like dextrose is being converted into substance which is poor in oxygen. This intramolecular oxygen derived from dextrose becomes available for carbon dioxid production and the requirement for inspired oxygen diminishes. Hence the volume of expired carbon dioxid may be greater than the volume of inspired oxygen. Max Bleibtreu[3] found that the respiratory quotient of a goose which had been stuffed with grain was 1.33, whereas the same goose when fasting showed a normal quotient for that condition of 0.728. Pembrey[4] describes how marmots previous to the winter hibernation instinctively devour large quantities of carbohydrate food, and how the respiratory quotient may rise even as high as 1.39. This indicates a fat production for use during the winter.

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[1] E. Voit: "Zeitschrift für Biologie," 1888, Bd. xxv, p. 543.

[2] Weinland: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 55; Bd. xliii, p. 86; 1903, Bd. xlv, p. 113.

[3] Bleibtreu: "Pflüger's Archiv," 1901, Bd. lxxxv, p. 345.

[4] Pembrey: "Journal of Physiology," 1901, vol. xxvii, p. 407.

Johansson, Billström and Heyl[1] have shown that if 50 to 200 grams of cane sugar be given a fasting man, the carbon dioxid output increases from 22.6 grams per half hour to about 30 grams per half hour. The larger ingestion does not produce a higher elimination of carbon dioxid than does the smaller amount. This indicates the evenness with which sugar entering the blood-stream is utilized by the organism. If sugar be present in excess it may be stored as glycogen until it is needed by the cells. The increased carbon dioxid output does not mean increased metabolism in the sense of increased heat production, but the increase due to the destruction of carbohydrates instead of fat in the production of the same amount of heat.

The truth of this is illustrated by Rubner's[2] experiment on a man in which he compared the production of energy in starvation with that produced after the ingestion of one and one-fifth that requirement in the form of cane sugar. For the sake of emphasis the metabolism after giving one and one-fifth the starvation requirement in the form of meat is also printed:

Starvation	2042 calories.
Sugar (120 per cent. of requirement)	2087 calories.
Meat (120 per cent. of requirement)	2566 calories.

It has been seen that carbohydrates ingested alone diminish the proteid metabolism. This reduces the specific dynamic action of proteid in the general metabolism and the small specific dynamic action of sugar scarcely changes the total metabolism from the starvation requirement.

Any excess of sugar above the requirement for energy is retained in the body either in the form of glycogen or as fat.

The contrast given above between the results of the ingestion of carbohydrates and of meat is extremely striking.

It is evident that the carbohydrate food protects proteid tissue from waste easier than other foodstuffs, and as a fuel is the most economical.

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[1] Johansson, Billström and Heyl: "Skan. Archiv für Physiologie," 1904, Bd. xvi, p. 263.

[2] Rubner: "Energiegesetze," 1902, p. 410.

When carbohydrates and proteid are ingested together in quantity sufficient for the requirement of the organism, it has been found that, taking the starvation proteid metabolism as one, nitrogen equilibrium can be maintained by ingesting one part of proteid.[1]

The work of Siven[2] however was the first indication that nitrogen equilibrium may be maintained at even a lower level than that ordinarily present in starvation. A somewhat undersized healthy man weighing 60 kilograms, who normally ate a mixed diet containing 16 grams of nitrogen, was given less and less proteid and an attempt was made to establish nitrogen equilibrium at lower and lower levels. The daily ration was rich in carbohydrates and yielded 2444 calories. This must have been considerably in excess of the requirement.

The experiment was divided into four periods of about a week each, which may be summarized as follows:

Length in Days.	N in the Food.	Days until N Equilibrium was Obtained.	N loss before N Equilibrium was Obtained.	Total N to Body.
I, 7	12.69	1	0.53	+9.73
II, 8	10.40	1	0.34	+6.04
III, 6	8.71	at once	...	+4.39
IV, 6	6.26	3	2.09	—0.58

It is apparent that nitrogen equilibrium may be established after ingesting 6.26 grams of nitrogen, although, as has been seen, the elimination during the early days of starvation in man is usually 10 grams. During the first three periods of reduced proteid intake, as much as 20.16 grams of proteid nitrogen were actually added to the body. In a fifth period nitrogen equilibrium was obtained on the fourth day on a diet containing 4.52 grams of nitrogen.

The susceptibility of the proteid metabolism to sudden withdrawal of carbohydrates was shown by Lusk[3] upon himself. Nitrogen equilibrium was nearly established in two different

[1] E. Voit and Korkunoff: *Loc. cit.*

[2] Siven: "Skan. Archiv für Physiologie," 1900, Bd. x, p. 91.

[3] Lusk: "Zeitschrift für Biologie," 1890, Bd. xxvii, p. 459.

experiments at different levels with the ingestion of 20.55 and 9.23 grams of nitrogen respectively. In the first experiment withdrawal of 350 grams of carbohydrates from the mixed diet caused a rise in nitrogen metabolism from 19.84 to 27.00 grams, incurring a loss of body nitrogen of 6.45 grams. In the second experiment withdrawal of the carbohydrates increased the nitrogen excretion from 11.44 to 17.18, a loss to the body of 7.95 grams. The losses are for the second day after the withdrawal of the carbohydrates, since the metabolism remains under the influence of the glycogen supply during the first day.

Subsequent experimentation has shown that *partial* replacement of carbohydrates by fat in the diet may have no influence, or only a transitory one, upon the amount of proteid metabolized. This is of value in practical dietetics. Tallquist[1] established nitrogen equilibrium in a man with a diet containing about 16 grams of nitrogen, 10 per cent. of the calorific value being contained in proteid and 90 per cent. in carbohydrates. On replacing one-third of the carbohydrate calories in the diet with fat calories an increased proteid metabolism was observed for two days, followed by nitrogen equilibrium on the third day. The food given contained 35 calories per kilogram, a moderate quantity, and was made up as follows:

Period I. 16.27 g. N + 44.6 g. Fat + 466 g. Carb. = 2866 Cal.
" II. 16.08 g. N + 140.1 g. Fat + 250 g. Carb. = 2873 Cal.

The nitrogen elimination was as follows:

Day.	N Excreted.	N Balance.
Period I.—1	17.11	—0.84
2	14.40	+1.86
3	14.65	+1.62
4	15.58	+0.69
" II.—5	17.66	—1.58
6	17.32	—12.4
7	15.94	+0.14
8	16.22	—0.14

This proves that with a diet containing 16 grams of nitrogen in proteid, nitrogen equilibrium is about as easily maintained on a mixed diet, including carbohydrates and fats, as when only carbohydrates are allowed with the proteid.

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[1] Tallquist: "Archiv für Hygiene," 1902, Bd. xli, p. 177.

Similar principles have been beautifully illustrated by Landergren.[1] Diets containing carbohydrates and fats but scarcely any nitrogen (about one gram daily), were given men and the proteid metabolism noted. This condition is called that of *specific nitrogen hunger.* After four days' administration of such a diet the urinary nitrogen may be reduced to less than four grams.

In one experiment in which this was accomplished carbohydrates were entirely replaced by fat with the result that proteid metabolism rose to the amount found in starvation (about 10 grams). It has already been explained that ingestion of fat alone will not affect proteid metabolism in starvation. The experiment is as follows:

Carbohydrate Period.		Fat Period.	
Diet = 45.2 Cal. per Kg.		Diet = 43.7 Cal. per Kg.	
	N in Urine.		N in Urine.
Day 0	*12.76	Day 5	4.28
" 1	....	" 6	8.86
" 2	....	" 7	9.64
" 3	....		
" 4	3.76		

* Ordinary diet.

On day 5, the first of the fat diet, it is evident that the proteid metabolism was affected by the use of the glycogen supply of the body, an influence which became negligible on the second and third days of the fat diet (p. 53).

Landergren gives the following results in various cases of specific nitrogen hunger, showing the nitrogen in the urine before the diet, and after four days thereof:

	II.	III.	IV.	V.
N in urine (ordinary diet)	12.76	11.87	13.7	15.2
N in urine (specific N hunger)	3.76	3.95	3.04	4.2
Calories in diet per kg	45.2	37.8	45.0	38.4

This reduction of proteid metabolism to four grams on the fourth day was brought about by the following diets in the different cases:

II. 750 g. carbohydrates............ = 45.2 cal. per kg.
III. 300 g. carbohydrates + 150 g. fat. = 37.8 " " "
V. 380 g. carbohydrates + 150 " " = 38.4 " " "

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[1] Landergren: "Skan. Archiv für Physiologie," 1903, Bd. xiv, p. 112.

A diet containing half its calories in carbohydrates and half in fat has therefore the same proteid protecting power as one made up of carbohydrates alone. This demonstrates the rationality of a mixture of the non-nitrogenous foodstuffs.

Landergren finds that on a diet containing two-thirds of the calorific requirement the urinary nitrogen on the fourth day may be eight grams, or nearly the fasting quantity. The diet was made up of—

X. 240 g. carbohydrate + 64 g. fat...... = 21.8 cal. per kg.

Therefore, in specific nitrogen hunger with undernutrition, the nitrogen eliminated in the urine appears to be increased. It is a pity that this statement rests on only one experiment, for it does not appear in accord with the following work of Chittenden.

Chittenden[1] finds that nitrogen equilibrium may be maintained on a diet containing a very small amount of proteid and two-thirds of the body's requirement of energy. The first experiment was on Fletcher and lasted six days. The daily ration contained 7.19 g. nitrogen + 38.0 g. fat + 253 g. carbohydrates = 21.3 calories per kg. The excreta contained 6.90 grams of nitrogen daily. On this diet the individual showed "remarkable physical strength and endurance."

Another experiment was performed by Chittenden on himself and lends itself for interesting comparison with the results of the ingestion of a maintenance ration. The food was principally vegetarian. The results may be thus tabulated:

A LOW LEVEL OF NITROGEN EQUILIBRIUM IN NORMAL AND UNDERNUTRITION.

Date.	Diet.		N Excretion.	N Balance.
	N in Grams.	Cal. per Kg.		
March 23	6.79	34.7	6.56	+0.23
March 25	6.88	22.4	6.34	+0.54

Nitrogen equilibrium may therefore be maintained at a low

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[1] Chittenden: "Physiological Economy in Nutrition," 1904, pp. 14, 40.

level even during the state of undernutrition present when 22.4 calories per kilogram are in the daily diet. On a milk diet Rubner[1] found that the ingestion of 2483 grams of milk containing 84 grams of proteid and two-thirds the body's requirement of energy resulted in the addition of 6.7 grams of proteid to the body daily for three days (p. 190).

It is a valuable piece of information to know that one may diet an obese patient on a food containing little proteid and two-thirds the body's energy requirement without danger of proteid loss. The other third of the necessary energy will be furnished by the body's own store of fat. It is not remarkable that the body is capable of great physical effort on such a diet, for a fasting man is also competent in this direction (p. 73).

In the last chapter mention was made of the sparing action of gelatin on proteid metabolism and its ingestion was found to prevent about 23 to 37.5 per cent. of the proteid loss during starvation. The sparing might be greater when gelatin was ingested with a mixed diet. To show this, J. R. Murlin[2] has experimented in the writer's laboratory on a man weighing seventy kilograms. The man starved three days, and then followed a period of three days during which nitrogen equilibrium was maintained on a diet containing the quantity of nitrogen eliminated during starvation. The proteid was supplied by beefsteak, oatmeal, and eggs, which, with cream and sugar, furnished a total of 3000 calories. Two-thirds of this total proteid nitrogen was then replaced by gelatin nitrogen for two days and the calories raised to 3400 by the addition of cane sugar. The result was that during the second day 0.06 gram of nitrogen were added to the body.

Murlin obtained the same results on a dog and also showed that three-quarters of the starvation nitrogen ingested as gelatin and one-quarter as proteid were not able to maintain nitrogen equilibrium. Two-thirds the starvation nitrogen requirement

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[1] Rubner: "Zeitschrift für Biologie," Bd. xv, 1879, p. 130.

[2] Murlin: Proceedings American Physiological Society, "American Journal of Physiology," 1905, vol. xiii, p. 29.

ingested as gelatin and one-third as proteid maintain nitrogenous equilibrium. Carbohydrates ingested alone reduce proteid metabolism to one-third that found in starvation. One-third the starvation quantity seems to be the limit of proteid metabolism compatible with life.

Since carbohydrates so effectively spare proteid from combustion it would seem logical that their use would render the retention of proteid in the body easier than when fat is given with proteid.

Lüthje[1] finds a long continued nitrogen retention in man when much nitrogen in proteid is ingested (up to 50 g. N daily!) and carbohydrates and fat making a total of 4000 calories or 66 calories per kilo. (See also Bornstein's experiment, p. 100.)

In a subsequent paper Lüthje[2] finds that the P_2O_5 retention in convalescence is that which corresponds to the retention of proteid as new tissue and for the upbuilding of the bones. Sometimes in a healthy person not enough P_2O_5 is retained to build up "flesh," and the proteid retained must therefore exist in the form of "deposit proteid." This proteid, he says, is not stored in the blood, for the composition of the blood does not alter; but is perhaps retained in the cellular fluids, just as glycogen is retained by the cells.

In conclusion, it may be said that carbohydrates are the most economical of the foodstuffs, both physiologically and financially. They are the greatest sparers of proteid. Ingestion of fat has for its object the relieving of the intestine from excessive carbohydrate digestion and absorption. Ingestion of fat in too large quantities leads to digestive disturbances and if carbohydrates are entirely abandoned, to acetonuria.

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[1] Lüthje: "Zeitschrift für klinische Medizin," 1902, Bd. xliv, p. 22.

[2] Lüthje: "Deutsches Archiv für klinische Medizin," 1904, Bd. lxxxi, p. 278.

CHAPTER VIII.

THE INFLUENCE OF MECHANICAL WORK ON METABOLISM.[1]

The source of mechanical work must be from metabolism, for mechanical energy cannot be derived from nothing. The necessary energy might be obtained in one of two ways, either at the expense of a proportionate reduction in the quantity of heat liberated by the resting organism, or by an increase in the amount of the metabolism. In the former case work would diminish the heat production, and might cool the tissues, which is not observed to take place. If work were done at the expense of increased metabolism, and if this increase were completely converted into mechanical effect, then the heat production in the organism might remain the same as in the resting state. If, however, the result of mechanical effort be a stimulation of metabolism to the extent of not only enabling the body to do work, but also causing it to produce more heat than when at rest, then the tendency of the tissues must be to grow warmer, perhaps with a resulting outbreak of sweat to reduce the body temperature through physical regulation. The last named is the actual process.

Lavoisier's discovery that the absorption of oxygen is increased during mechanical exercise, firmly established the fact of a higher metabolism under these conditions.

The first experiments in which the effect of work upon the total metabolism was demonstrated were made upon a man by Pettenkofer and Voit.[2] A man turned an ergostatic wheel

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[1] In the account of metabolism during starvation, a short description has already been given of the influence of mechanical work on proteid metabolism, of the influence of posture on general metabolism, and of the relation of the amount of metabolism to the diurnal variations of human temperature.

[2] Pettenkofer and Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 538.

7500 revolutions on each of the working days for a period of nine hours, affording sufficient exercise to cause great fatigue at the end of the day. The experiments were made both during hunger and when the man was ingesting a medium mixed diet. The food supplied in the mixed diet contained:

	Grams.	Calories.
Proteid	121.7	506
Fat	117.	1088
Carbohydrates	352.	1443
Total		3037

The metabolism of the strong workman, weighing seventy kilograms, at rest and at work, starving or on the medium mixed diet as given above, is presented in the following table:[1]

EFFECT OF MECHANICAL WORK ON METABOLISM IN MAN.

	Grams Metabolized.					
	Proteid.	Fat.	Carbohydrates.	Cal. of Metabolism.	Cal. above Fasting Quantity.	Experiment No. of Pettenkofer and Voit.
Starvation—Rest	70.8	222		2374		I
" —Rest	68.7	208		2231		III
" —Work	66.1	387		3882	1582	IV
Mixed Diet—Rest	121.7	73	352	2638	336	V
" —Rest	118.7	93	352	2714	412	VI
" —Rest	125.0	84	352	2750	458	VII
" —Work	121.7	208	352	3856	1554	VIII
" —Work	122.0	152	352	3378	1076	IX

From these early experiments it was evident that mechanical work did not increase proteid metabolism even in starvation,

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[1] I have multiplied the nitrogen of the ingesta and egesta by 6.25 to obtain the quantity of the proteid given and metabolized. The ratio N:C = 1:3.28 in proteid has been employed. The dry starch has been calculated as containing 44.2 per cent. and the fat as containing 76.5 per cent. of carbon, which were the figures used by Pettenkofer and Voit. Rubner's standard calorimetric values have been used. (See Introductory Chapter.)

but that the power to do work might readily be supplied by the increased metabolism of fat.

It is interesting to note the increase of the metabolism above the fasting minimum under the above circumstances. This relation is embodied in the following table:

	Calories of Metabolism.	Increase.
Starvation—Rest (average)	2302	
" —Work	3882	1582
Medium diet—Rest (average)	2717	415
" —Work	3856	1554
" —Work	3378	1076

This table indicates a specific dynamic action of the food amounting to 415 calories. Another conclusion may be drawn from the table, and one which, if true, is of importance; it is that *during the working days the specific dynamic action of the food does not appear*. In other words the metabolism during work on a mixed diet is not greater than during starvation when the same amount of work is being effected. It may be that the free heat liberated as the result of the specific dynamic action of the food can be utilized in warming the cells in the service of the production of mechanical energy, just as it is used in lieu of the heat produced through chemical regulation. If this be true, giving proteid to men at work—for example, athletes—would not entail economic waste of the fraction usually lost when it is given during rest.

Rubner in his "Energiegesetze" writes that he is investigating the influence of work on metabolism, and it may be assumed that this problem has already been solved. The writer merely advances the above as a suggestion of possibilities.

Rubner[1] shows that a man of seventy kilograms weight, developing mechanical energy to the extent of 15,000 kilogrammeters per hour, produces practically the same quantity of carbon dioxid, no matter what the temperature of his environment may be. The results of the experiment are as follows:

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[1] Rubner: Von Leyden's Handbuch, "Die Ernährungstherapie," 1903, Bd. i, p. 74.

Temperature of the Air.	Percentage Moisture in the Air.	Carbon Dioxid per Hour in Grams.	Water Excreted per Hour in Grams.
7.4°	81	84.0	58.0
12.7°	84	78.5	70.8
16.7°	59	97.0	138.1
17.5°	87	84.5	90.4
18.8°	83	81.2	112.8
25.0°	47	78.7	230.0

This person while at rest and at a temperature of 21.1° excreted 33.6 grams of carbon dioxid and 42 grams of water.

It is clear that during work the metabolism is independent of surrounding temperature, of climatic conditions. In other words, *during mechanical work the influence of the chemical regulation of body temperature may be eliminated.* The extra heat production in doing mechanical work is utilized instead of the production of heat which is excited reflexly through cold.

Generally speaking, neither clothing nor temperature affect the amount of the metabolism during exercise. They influence only the quantity of water eliminated in the perspiration, in the effort of the body to maintain its normal temperature through physical regulation. It is evident from Rubner's details of the water excretion that at a low temperature the extra heat production during mechanical exercise is lost by radiation and conduction. Rubner explains that the slight increase in the excretion of water above that lost while at rest, is due to its increased evaporation through increased respiratory activity. At a higher temperature conduction and radiation become insufficient to cool the body, and a large proportion of the loss of heat takes place at the expense of the evaporation of sweat.

In hot, moist climates, however, the cooling of the body through the evaporation of moisture becomes difficult, and this is especially pronounced in the case of fat people (p. 94), who with difficulty discharge the heat produced within them. Broden and Wolpert[1] show the effect of the action of temperature and humidity on the metabolism of a fat man, weighing 101 kilograms, who executed the same amount of mechanical work

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[1] Broden and Wolpert: "Archiv für Hygiene," 1901, Bd. xxxix, p. 298.

under various conditions of experimentation. The work was light, being 5375 kilogrammeters per hour. The results were as follows:

EFFECT OF WORK, TEMPERATURE, AND HUMIDITY ON THE METABOLISM OF A FAT INDIVIDUAL.

Temperature.	Grams per Hour.			
	Dry Air.		Humid Air.	
	CO_2 in Grams per hour.	H_2O in Grams per hour.	CO_2 in Grams per hour.	H_2O in Grams per hour.
20°	47.8	..	46.4	
28–30°	47·3	..	48.0	
36–37°	50·3	319 + 38 g. sweat.	60.7	269 + 266 g. sweat.

This individual was the same already mentioned, p. 94, and the explanation given there is equally applicable here. In a dry climate the same amount of mechanical work may be accomplished by a fat person at both 20° and 30° without changing the metabolism. At a temperature of 37° the metabolism rises, for the cooling power of the evaporating sweat does not seem sufficient to act through the dense covering of fat. This action is intensified in moist air where the evaporation of water is hindered. Under these latter conditions the small amount of work was accomplished only at the expense of great discomfort and profuse perspiration.

The obese therefore work under great disadvantage in a hot, and especially in a hot and moist, climate. The profuse perspiration explains their desire for water to drink.

In the early experiments of Pettenkofer and Voit, already cited, it was shown that work did not raise the proteid metabolism even in starvation, and that the source of the power appeared to be derived from the increased combustion of the non-nitrogenous fat.

In other experiments a slight rise in the nitrogen metabolism, continuing into the day following work, has been noted. The proteid metabolism, however, is not sufficient to yield the energy necessary for a hard day's work. In the well known experiments of Fick and Wislicenus[1] the authors climbed the Faulhorn, in Switzerland, a mountain 1956 meters high. The product of their weight into the height to which they raised themselves gave them the work done. The proteid metabolism, as calculated from the nitrogen in the urine during the walk and seven hours thereafter, could have afforded only a third of the necessary energy for the ascent of the mountain. The experimenters took their last nitrogenous food seventeen hours before starting on their walk. They climbed for six hours and collected the urine of this period and that of seven hours thereafter. Their results were as follows:

	URINARY N OF 13 HRS.	DYNAMIC VALUE OF N IN KGM.	BODY WEIGHT.	HEIGHT OF FAULHORN.	WORK IN KGM.
Fick........	5.74	63,378	66	1956 meters.	129,096
Wislicenus ..	5.54	61,280	76	1956 meters.	148,656

The work accomplished was far in excess of the energy liberated from the proteid metabolism of the time. The output of energy as measured above was not all the increase in the amount of mechanical energy during the period, for the heart and respiratory muscles acted with greater force, and energy was expended by swinging the arms and by friction on the road.

The fact observed by Pettenkofer and Voit that proteid metabolism may not be appreciably affected during mechanical work has been abundantly confirmed by Krummacher.[2] A porter weighing 79 kilograms was given a diet containing 3700 calories, 14.28 grams of proteid nitrogen and a large amount of carbohydrate. The man turned a dynamometer and produced 402,000 kilogrammeters of work. The slight increase

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[1] Fick and Wislicenus: "Myothermische Untersuchungen," 1889.

[2] Krummacher: "Zeitschrift für Biologie," 1896, Bd. xxxiii, p. 108.

in proteid metabolism could have yielded but three per cent. of the energy required for the work. Krummacher states that proteid metabolism may increase during work only when the non-nitrogenous fat and carbohydrates become less available in metabolism. We have already seen that proteid metabolism rises in the absence of carbohydrates. It may be that with the exhaustion of carbohydrates during exercise, a period ensues when the loss of their influence leads to an increased proteid destruction. The larger the quantity of carbohydrate given the less marked would be this influence. It is interesting in this connection that soldiers when starting on a march may have a high respiratory quotient (indicating the combustion of carbohydrates) which falls at the end of the march (fat combustion) and which may remain lower than at first, even on a day following the march.[1] The fact that mechanical work may be accomplished at the expense of an increased combustion of fat and carbohydrate should not cause one to forget that proteid *may* become the sole source of energy in the body. It has already been shown that a fasting animal, after burning all his fat, maintains his life on proteid alone (p. 66), and that Pflüger kept a dog in active condition on meat alone. As proteid may yield 58 per cent. of sugar, this substance may still be the principal source of energy.

Bornstein[2] reports continual retention of ingested proteid during seventeen days' work, at a time when there was no fat retention. The quantity of proteid given was large, containing 19.96 grams of N, and the daily work accomplished was moderate, being 17,000 kilogrammeters. The nitrogen retention amounted to 1.475 grams daily, or an addition of 800 grams of "flesh" to the body in seventeen days.

Loewi[3] reaches the same conclusion that long continued muscular exercise favors proteid retention. This suggests the basis of muscular hypertrophy due to physical exercise.

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[1] Zuntz and Schumburg: "Physiologie des Marsches," 1901.

[2] Bornstein: "Pflüger's Archiv," 1901, Bd. lxxxiii, p. 540.

[3] Loewi: "Archiv für Physiologie," 1901, p. 299.

Large proteid ingestion, however, is not apparently essential to the full maintenance of physical power. This has been shown by Chittenden[1] who maintained soldiers and athletes in physical training for months at a time on diets containing between seven and ten grams of nitrogen, or about half what the average man takes if the question be left to his taste (see p. 179).

It is evident that the power to accomplish muscular work is not usually derived from proteid metabolism, but from the combustion of the non-nitrogenous sugar and fat.

Therefore, physical exercise requiring fat consumption without concomitant destruction of proteid must be of the greatest value in the treatment of obesity.

The problem at once arises: What is the relative value of fats and carbohydrates as fuel for the production of mechanical energy by the body?

Zuntz,[2] from experiments made by Heineman, calculates that when carbohydrates predominate in a man's diet an amount of energy above the resting requirement is liberated which equals 9.33 calories for every kilogrammeter of work accomplished, whereas when fat is given 10.37 calories are liberated in the performance of the same amount and the same kind of work. The work was done by turning the wheel of an ergostat. Since one kilogrammeter is the mechanical equivalent of 2.35 calories, it is evident that 25 per cent. of the total excess of energy developed by work is convertible into mechanical effect, the balance being dissipated as heat. Similar experiments made by Zuntz on himself showed that 9.39 and 9.33 calories of metabolism were liberated on a fat diet, 10.37 and 10.41 on a carbohydrate diet, when one kilogrammeter of work was accomplished.

There seems to be little difference in the efficacy of the body as a machine, whether fat or carbohydrates are used as fuel.

Heineman[3] remarks that Chauveau's idea that fat must be first converted into sugar before being available for mechanical

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[1] Chittenden: "Physiological Economy in Nutrition," 1905.

[2] Zuntz: "Pflüger's Archiv," 1900, Bd. lxxxiii, p. 557.

[3] Heineman: *Ibid.*, p. 476.

work can scarcely be valid, for such a conversion of fat carbon into sugar would entail a minimum loss of energy available for mechanical work of 29 per cent.

Atwater and Benedict[1] claim to have confirmed these results, although unfortunately the diets provided were not strictly fat-proteid and carbohydrate-proteid, but were really mixed diets.

Thus J. W. C., during two periods of twenty-two days each, ingested each day diets which produced the following metabolism as calculated from the body's excreta:

CALCULATED METABOLISM.

	PERIOD I. CARBOHYDRATE DIET.	PERIOD II. FAT DIET.
Proteid	434 calories.	489 calories.
Fat	1288 "	3190 "
Carbohydrates	3371 "	1465 "
Total metabolism	5093	5144

The average of work accomplished and body heat evolved each day, as measured in the Atwater calorimeter, were as follows:

WORK AND METABOLISM AS DIRECTLY MEASURED.

	CARBOHYDRATE DIET.	FAT DIET.
Mechanical work	543 calories.	550 calories.
Body heat	4593 "	4555 "
Total metabolism	5136	5105

The work was done on a stationary bicycle. It is evident that the work could not have been at the expense of proteid metabolism. But it is also plain that the work could have been derived from carbohydrate combustion even on the "fat" diet of Period II.

These experiments, however, were the first to demonstrate exactly that mechanical work was done at the expense of a dynamic equivalent of metabolism,—a splendid confirmation of the law of the conservation of energy.

In one other experiment Atwater and Benedict calculated for J. W. C. a metabolism amounting to 9981 calories, divided as follows: Proteid, 478 calories; fat, 7744 calories; carbohy-

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[1] Atwater and Benedict: "Experiments on the Metabolism of Matter and Energy in the Human Body," 1903, U. S. Dept. of Agriculture, Bulletin 136.

drates, 1759. The man worked for sixteen hours on the bicycle. The work done measured an equivalent of 1482 calories; the body heat production was 7382 calories, both of which were measured in the Atwater calorimeter, and the total energy loss reached 9314 calories,[1] a height of metabolism attained also by Maine lumbermen[2] actively employed (p. 187).

Although from Zuntz's work it seems proved that, in furnishing power for mechanical work, carbohydrates and fat are replaceable one for the other according to their dynamic values, there is a well-founded belief that work may be obtained in larger quantity from an individual if carbohydrates be available. Schumburg[3] finds that ingestion of carbohydrates enables a fatigued muscle to contract more powerfully. Hellesen[4] states that in doing mechanical work in the morning before breakfast, an improved capacity occurs thirty to forty minutes after ingesting sugar.

The ready exhaustion of diabetics who cannot burn dextrose confirms this observation.

Lee and Harrold[5] have found evidences of great fatigue in the excised muscles of a cat from which the readily combustible sugar had been removed by rendering the cat diabetic with phlorhizin. A cat treated similarly, but whose organism had been flooded with sugar by ingestion before killing the animal, showed a much larger capacity for muscular contraction.

The writer[6] while injecting phloretin solutions into the jugular vein of fasting rabbits, diabetic through phlorhizin, noticed that seven out of eight rabbits had convulsions, while normal rabbits were not so affected. Four died and three lost motor control of the muscles of their limbs. In these three

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[1] The calories calculated from the metabolism and those directly measured by the calorimeter did not exactly agree in this particular instance—an exception in a brilliant series.

[2] Woods and Mansfield: U. S. Dept. of Agriculture, 1904, Bulletin 149.

[3] Schumburg: "Archiv für Physiologie," 1896, p. 537.

[4] Hellesen: "Skan. Archiv für Physiologie," 1904, Bd. xvi, p. 139.

[5] Lee and Harrold: Proceedings of the American Physiological Society, "American Journal of Physiology," 1900, vol. iv, p. ix.

[6] Lusk: "Zeitschrift für Biologie," 1898, Bd. xxxvi, p. 109.

there was an increased dextrose elimination in the urine on account of the passage of the glycogen content of the organs into the blood, which glycogen would normally be immediately available for muscular activity (p. 71). The animals which survived the convulsions obtained control of their muscles in two to four hours. This indicates a slow preparation from fat of materials available for the production of muscle work.

Schumburg[1] finds that coffee and tea have no recuperative power over the muscles of a fatigued organism, except when taken with other foods, and that the stimulating action of alcohol is only temporary. Hellesen,[2] exercising before breakfast, finds that the effect of taking tea is almost negligible, and that the effect of alcohol is at first to increase the muscle power but that after twelve to forty minutes there is a decrease in power which lasts for two hours. No such depression occurs after taking sugar. It is obvious that alcohol is not beneficial when muscular work is to be accomplished.

The carbon dioxid produced as a result of mechanical work is quickly eliminated through the lungs. Higby and Bowen[3] find that the increased elimination begins twenty seconds after the commencement of bicycle riding and reaches its maximum in about two minutes. At this point it remains constant from minute to minute provided the same amount of work is done. This principle has been frequently demonstrated by Zuntz and his pupils. It is evident, however, that the quantity of carbon dioxid excretion for the unit of work accomplished will be less during starvation and on a fat diet than when carbohydrates are ingested, by reason of the higher heat value of fat carbon.[4]

It has already been shown that 25 per cent. of the total energy of the increase above the resting metabolism as caused by work is converted into mechanical energy by a person turning the wheel of an ergostat with his arms.

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[1] Schumburg: *Loc. cit.*

[2] Hellesen: *Loc. cit.*

[3] Higby and Bowen: "American Journal of Physiology," 1904, vol. xii, p. 335.

[4] Johansson and Koraen: "Skand. Archiv für Physiologie," 1902, Bd. xiii, p. 251.

Katzenstein[1] has shown a still more economical utilization of the fuel when the work accomplished is climbing, about 35 per cent. of the total increase in metabolism being then converted into mechanical effect. Walking, the commonest muscular exercise, is accomplished with the greatest economical efficiency.

A great many interesting details have been worked out in Zuntz's laboratory by his pupils. The following epitome of long investigations shows the comparative energy equivalents necessary for a dog, horse, and man to move one kilogram of body weight one meter with a given rapidity along a horizontal plane or to lift one kilogram of body weight one meter high.[2] The experiments were made by placing the individual on a moving platform, the speed and incline of which could be varied.

ENERGY REQUIREMENTS OF DIFFERENT ANIMALS IN PERFORMANCE OF THE SAME AMOUNT OF MECHANICAL WORK.

Animal.	Weight.	Energy Requirement in Kilogrammeters.		Velocity in Meters per Minute of horizontal movement.	Incline of road in per cent. during Climbing Experiment.
		For moving horizontally 1 Kg. 1 Meter.	For raising 1 Kg. 1 Meter high.		
Dog	26.9	0.495	2.954	78.57	17.2
Dog	26.9	0.501	3.259		
Horse	456.8	0.137	2.912	78.57	10.3
Man	55.5	0.334	2.857	74.48	9.6–13.3
"	72.9	0.217	3.190	71.32	6.5
"	67.9	0.211	3.140	71.46	
"	80.0	0.288	3.563	51.23	30.7–62
"	88.2	0.263	3.555	42.34	
"	72.6	0.284	2.913	62.04	23–30.5
"	81.1	0.231	2.912	60.90	
"	80.0	0.244	2.729	56.54	
F. Normal locomotion	86.5	0.219	2.746	66.94	23.3
F. Slow locomotion	86.5	0.233		35.92	
R. Normal	68.5	0.230	2.846	63.95	
R. Slow	68.5	0.251		34.58	

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[1] Katzenstein: "Pflüger's Archiv," 1891, Bd. xlix, p. 379.

[2] Frentzel and Reach: *Ibid.*, 1901, Bd. lxxxiii, p. 494.

A study of the foregoing table will show that it requires much less energy for a horse to move one kilogram of his weight one meter horizontally than for a dog to do the same at the same velocity. It also appears that a man of small weight requires more energy to a unit of substance than a man of large size. This rule has been confirmed in dogs by Slowtzoff,[1] who shows that energy amounting to 0.529 kilogrammeter is required for one meter horizontal motion by a dog weighing 37 kilograms and 1.138 kilogrammeters by a dog weighing 5.5 kilograms. Slowtzoff does not find that this variation is proportional to the skin area of the animal.

The table also shows that there is little variation in the dog, horse and man in the amount of energy necessary to raise one kilogram of body substance one meter high.

It is possible to calculate the food ration for a march if the figures given in the table be employed. If it be assumed that a man weighing 70 kilograms travels 74.4 meters a minute he will accomplish 4.46 kilometers or 2.7 miles per hour. If it requires the energy equivalent of 0.217 kilogrammeters to move one kilogram of his weight one meter it will require 67,747 kilogrammeters (0.217 × 70 × 4460) to move him 4.46 kilometers,—67,747 kilogrammeters being equivalent to 159.205 calories. This is the equivalent of 17.1 grams of fat which may be added to the maintenance resting dietary requirement to supply the energy necessary for an hour's quiet walk on a level road. If the road be inclined so that the man raises himself 500 meters during the hour's walk, the metabolism will be still further increased. The work of ascent will be his weight multiplied by the height of his climb, or 35,000 kilogrammeters. The expenditure of energy by the body in order to accomplish this work is threefold the work done, or 105,000 kilogrammeters, which equals 246.750 calories, or 26.5 grams of fat. The hour's walk in this case would require the production of an energy equivalent, above the resulting metabolism, amounting to that contained in 43.6 grams of fat,—that is, 17.1 grams for a forward locomotion

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[1] Slowtzoff: "Pflüger's Archiv," 1903, Bd. xcv, p. 190.

of 4.46 kilometers and 26.5 grams to lift the body to an altitude of 500 meters.

In the last-mentioned table it is seen that there is an increase in the metabolism for a unit of horizontal motion when the progress of the individual is very slow. This is explained by the fact that speed of progress was half the normal, was unusual, and forced.

The rule is that the metabolism increases with speed in men (0.39 to 0.84 per cent. per meter increase between 60 and 100 meters per minute) and in horses (1.03 per cent. per meter increase above 78 meters per minute), but this is not seen in dogs.[1]

Katzenstein[2] finds that the metabolism during the descent of a mountian is less by 10 per cent. than the increase caused by walking on a level surface. The muscles which act to inhibit a too rapid descent are not required to be so active as those which give forward impetus to the body on a level road.

This idea has recently been still further investigated by mountaineers[3] who compared the actual heat production with the energy of metabolism during one minute, for horizontal motion, and for ascent and descent of a mountain path which had a 25 per cent. incline. The results were as follows:

	ASCENT 28.8 METERS.	HORIZONTAL 100 METERS.	DESCENT 76 METERS.
Calories of energy of metabolism...........	69.3	67.8	40.8
Calories of heat liberated.....................	46.9	67.8	85.5

The smallest liberation of heat occurred during the ascent of the mountain at the time when the energy of metabolism was being converted into energy of position.

The largest heat production occurred during the descent of the mountain. The metabolism was the least, but energy of position was converted into heat through the vibration of the body at each footfall.

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[1] Zuntz: "Pflüger's Archiv," 1903, Bd. xcv, p. 192.

[2] Katzenstein: *Loc. cit.*, p. 376.

[3] Zuntz, Loewi, Müller, and Caspari: "Höhenklima und Bergwanderungen in ihrer Wirkung auf den Menschen," 1906.

Zuntz and Schumburg[1] show that a well-placed knapsack is carried by a soldier with very little increased expenditure of energy. A soldier weighing 74.45 kilograms, moving at the rate of 74.4 meters per minute, requires 541.8 calories for the movement of one kilogram of substance 1000 meters. The same soldier, laden with a knapsack weighing 19 kilograms (total weight=93.45 kilograms), requires only 502.3 calories to move one kilogram 1000 meters. A pack may therefore be more economically moved than the body's substance, which is an argument against obesity.

If the knapsack be badly placed, or if the body be sore and weary, Zuntz and Schumburg find an increase in the metabolism of a marching soldier.

Lavonius[2] finds the maximum amount of work attainable from a trained wrestler of great reputation to be the equivalent of 30 kilogrammeters per second.

A subject of very great interest is the result of training. It is well known that if a cobbler, for example, be removed from his trade and be compelled to climb a mountain, he will at first be of little use as compared with a Swiss guide. But after constant practice the blood-vessels open at once in response to the needs of the muscles and the heart expends less energy; unnecessary motions with the arms and legs are diminished in number; the strain for the accomplishment of a given piece of work diminishes; the thorax enlarges to promote readier respiration; the man becomes "trained," and there may be a lessened metabolism for the fulfillment of a definite amount of work.

The experimental measurements of the efficacy of the working organism as described above were made on well-trained men, a difference on account of training having been early recognized by Zuntz.

Certain differences between the urine of trained and untrained men have already been noted (p. 63).

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[1] Zuntz and Schumburg: "Studien zu einer Physiologie des Marsches," Berlin, 1901.

[2] Lavonius: "Skan. Archiv für Physiologie," 1905, Bd. xvii, p. 196.

Bürgi[1] made some investigations upon an individual before and after training for mountain climbing. The ascents were made at different altitudes on the roadbed of mountain railways, and the carbon dioxid elimination was measured. The results are shown in the following table:

EFFECT OF "TRAINING" ON METABOLISM.

Place.	Altitude in Meters.	Incline of Road in per cent.	CO_2 Excretion per Kgm. of Work.	
			Untrained.	Trained.
Brienz	620	17.29	2.430	2.103
Gornergrat	2987	19.3	2.711	2.268
Brienz	690	19.0	2.251	2.063
Gornergrat	3021	19.3	2.445	2.117

It is evident from this that a trained mountaineer accomplishes his work at the expense of less metabolism than when untrained. Also that at a moderately high altitude (3000 meters = 522 mm. of mercury, barometric pressure) the trained organism is as efficient for mechanical work as at the sea level; whereas the untrained man requires a much greater metabolism to accomplish a unit of work at the higher altitude than at the lower.

At still higher altitudes there is always an increase in the amount of metabolism necessary to accomplish mechanical effort, and this will be discussed in another chapter.

Another fact of importance is that the effect of training especially affects the muscles involved in the particular movement, and not those which do not contract. Thus Zuntz[2] found that a dog trained for horizontal motion on a level street required 1179 small calories to move one kilogram body weight 1000 meters and 7.668 small calories to raise one kilogram body weight one meter high. The dog was then gradually trained to ascend an incline. After two years he required only 5.868 small calories

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[1] Bürgi: "Archiv für Physiologie," 1900, p. 509.

[2] Zuntz: "Pflüger's Archiv," 1903, Bd. xcv, p. 200.

to lift one kilogram one meter, but he required 1343 small calories per kilogram for horizontal locomotion through 1000 meters. Therefore the specifically trained muscles work more economically than those which are at the time but little used.

A man trained for mountaineering will often find himself uncomfortable when walking on a level road. The mountaineer will not find the bicycle an easy means of locomotion,[1] nor will the bicyclist unscathed essay the mountain.

A benefit derived from riding a horse is the shaking of the internal organs, which is also achieved by descending a steep pathway. This may be beneficial to the life processes in such a comparatively immobile organ as the liver for example. It also appears to promote a freer evacuation of the bowels.

In swimming there is considerable respiration gymnastics.[2] The water pressure upon the thorax is the equivalent of the weight of an 8-kilogram sand-bag, which the swimmer seeks to counterbalance by increasing the pressure in his lungs through puffing with his lips. By turning over on the back the swimmer removes this respiratory influence. Cold water stimulates metabolism (p. 93), but the effect of the salt in ordinary sea water is certainly negligible.

There can be little doubt that exercise, especially in the open air, strengthens the organism and therefore tends to prolong life. Sometimes muscular exercise is mistakenly considered as favoring intellectual activity. Yet college presidents are not selected from the ranks of prize-fighters.

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[1] Concerning work expended in bicycle riding see Berg, Du Bois-Reymond and L. Zuntz: "Archiv für Physiologie," Supplement, 1904, p. 20.

[2] R. du Bois-Reymond, *Ibid.*, 1905, p. 253.

CHAPTER IX.

A NORMAL DIET.

The principles of metabolism have been sufficiently explained in the foregoing chapters to make it possible to understand the basis of a diet which shall be physiologically rational.

It has been seen that the average starvation metabolism of a vigorous man at light work and weighing 70 kilograms approximates 2240 calories, or 32 calories per kilogram. It is obvious that this quantity of energy must be contained in the daily food, and a little more to counterbalance the "specific dynamic" or heat-increasing power of the foodstuffs, if the individual is to be maintained in calorific equilibrium. It has been seen that when an average mixed diet is ingested the maintenance requirement is between 11.1 and 14.4 per cent. above the starvation minimum (p. 139). This would amount to from 2488 to 2562 calories, or from 35.5 to 36.6 calories per kilogram of body weight in the case of the individual just referred to.

Since man through clothing shuts himself off from the reflex action of cold on the skin, the greatest factor which tends to increase his metabolism is mechanical work, and the total calories required are here dependent on the kind and the amount of the work accomplished. The requirements in this regard have already been discussed.

A point of great interest is that of the proper proportion in which the individual foodstuffs should be put together in making up a ration.

Voit defines a food as a well-tasting mixture of foodstuffs in proper quantity and in such a proportion as will least burden the organism. What is the proper proportion?

Voit[1] gives the following ration for the use of an average

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[1] Voit: "Physiologie des Stoffwechsels," 1881, p. 519.

laborer, such as a soldier in a garrison,—that is, for a man at work from eight to ten hours a day: Proteid, 118 grams; carbohydrates, 500 grams; fat, 56 grams. This diet contains 3055 calories.

The allowance of 118 grams of proteid has provoked much discussion. The original figures were obtained by Voit by averaging the proteid metabolism of many laboring men. This requirement of proteid was therefore obtained by the statistical method, which simply showed what the average laborer in habit destroyed. For the same class of artisan, the diet given by Rubner calls for 127 grams of proteid; by Atwater 125 grams; and Lichtenfelt[1] confirms Voit's average as being the quantity of proteid taken by laborers in northern Italy.

For men at hard labor, such as soldiers in the field, even higher quantities of proteid are commended,—by Voit, 145 grams; by Rubner, 165 grams; by Atwater, 150 grams. These figures again are based on statistics. Quite recently Woods and Mansfield[2] found that the average proteid in the ration of fifty lumbermen is 164.1 grams.

In striking contrast to this Siven[3] at the age of thirty-one and a half years and weighing 65 kilograms, finds he can maintain himself in nitrogen equilibrium for a short period on a diet containing between 4 and 5 grams of nitrogen, or 25 to 31 grams of proteid. In fact, in one experiment the food contained 4 grams of nitrogen, of which 2.4 grams only were in 15.4 grams of true proteid and the balance in amino acids and other nitrogenous non-proteid matter of vegetable origin. Here nitrogen equilibrium was nearly attained, the nitrogen ingested being 4, and that excreted 4.28 grams. The food given, which was rich in carbohydrates, contained 2717 calories, or 43 calories per kilogram, and the total metabolism as estimated by respiration experiments indicated a heat production of 2082 or 32 calories per

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[1] Lichtenfelt: "Pflüger's Archiv," 1903, Bd. xcix, p. 1.

[2] Woods and Mansfield: "Studies of the Food of Maine Lumbermen," U. S. Department of Agriculture, 1904, Bulletin 149.

[3] Siven: "Skan. Archiv für Physiologie," 1901, Bd. xi, p. 308.

kilogram. Here was practically nitrogen equilibrium maintained at the minimum level, and a low total metabolism which was largely at the expense of carbohydrates.

It will be recalled that the quantity of nitrogen in the urine in the average fasting man who has been previously well nourished, is 10 grams, a minimum which is only reducible by carbohydrate ingestion.

The experiments of Siven did not satisfy people that a low proteid metabolism was compatible with continued health and strength. Munk[1] and Rosenheim[2] both found that dogs given a quantity of proteid sufficient only to maintain nitrogen equilibrium gradually lost strength and became afflicted with digestive disturbances. These experiments fortified the idea of the benefits to be derived from a diet containing more proteid than was necessary for the maintenance of nitrogen equilibrium—a *luxus* consumption. Rubner declares that a large proteid allowance is the right of civilized man.

The tradition that a continued liberal allowance of proteid in a diet is a prerequisite for the maintenance of bodily vigor has been dispelled by Chittenden[3] and his co-workers, of whom Mendel is the most prominent.

Professor Chittenden had suffered from persistent rheumatism of the knee-joint and determined on a course of dieting which should largely reduce the proteid and the calorific intake. The rheumatic trouble disappeared, and minor troubles such as "sick headaches," and bilious attacks no longer recurred periodically as before. "There was a greater appreciation of such food as was eaten; a keener appetite and more acute taste seemed to be developed, with a more thorough liking for simple foods." During the first eight months of the dieting there was a loss of eight kilograms of body weight. Thereafter for nine months the body weight remained stationary. "Two months of the time were spent at an inland fishing resort, and during a

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[1] Munk: "Archiv für Physiologie," 1891, p. 338.

[2] Rosenheim: *Ibid.* p. 341.

[3] Chittenden: "Physiological Economy in Nutrition," 1904.

part of this time a guide was dispensed with and the boat rowed by the writer frequently six to ten miles in a forenoon, sometimes against head winds (without breakfast) and with much greater freedom from fatigue and muscular soreness than in previous years on a fuller dietary."

During the period of nine months the nitrogen of the urine was determined daily. The average was 5.69 grams. During the last two months and a half, the average elimination was 5.40 grams for a body weight of 57.5 kilograms. Experiments showed that about one gram of nitrogen was eliminated in the feces and that nitrogen equilibrium could be maintained with dietaries of low calorific values (1613 and 1549 calories = 28 and 27 calories per kilogram) containing 6.40 and 5.86 grams of nitrogen. These figures correspond to diets containing 40.0 to 36.6 grams of proteid instead of the 118 grams honored by habit and tradition. Professor Chittenden proclaims such a diet as of the highest importance to health.

The case of Chittenden recalls a note from an early convert to the "Graham system" of vegetarianism. Sylvester Graham, in 1829, began the advocacy of moderation in the use of a diet consisting of vegetables, Graham bread (made of unbolted flour), fruits, nuts, salt and pure water, and excluding meat, sauces, salads, tea, coffee, alcohol, pepper, and mustard. The letter reads as follows:[1] "The first three months of my experiment on the Graham system was attended by a loss of 20 to 30 pounds of flesh. Some of my neighbors expostulated with me,—told me I should destroy myself by starvation, and it was even reported in a neighboring town that I had actually died from that cause. But my appetite was increasingly good and my health was increasing, and in a short time my headaches, colds, costiveness, and rheumatism left me entirely, together with my hypochondriacal and gloomy state of mind, and have not returned since, notwithstanding I have been as much exposed to wet and cold as at any period of my life."

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[1] Charles Clapp: "The Graham Journal of Health and Longevity," Boston, 1837, vol. i, p. 57.

Chittenden's experiments were not confined to an individual nor to a single group of individuals. Other experiments were made on professional men, on student athletes in training, and on soldiers under military *regime.* The daily nitrogen in the urine in periods extending from five to nine months averaged as follows in the individuals belonging to the three groups:

Professors and Teachers.		University Athletes.		United States Soldiers.	
Weight in Kg.	N in Urine in G.	Weight in Kg.	N in Urine in G.	Weight in Kg.	N. in Urine in G.
57.0	5.69	71.0	9.37	62	7.42
70.0	6.53	61.0	10.41	59	7.03
65.0	7.43	78.0	8.88	60	7.26
65.0	8.99	83.0	9.04	58	8.17
61.5	8.58	62.0	7.47	60	8.39
		56.0	7.58	53	7.13
		73.0	10.09	71	8.91
		75.0	11.06	72	7.84
				62	8.05
				59	7.38
				55	8.25
				65	8.08
				57	8.61

At convenient periods during the above experiments it was determined that the body was being maintained in nitrogenous equilibrium on the diet which gave rise to the above amounts of urinary nitrogen (p. 157).

The professional group alleged a greater keenness for its work, the athletic group won championships in games, and the soldiers maintained perfect health and strength, many professing repugnance to meat when they were allowed it after five months of practical abstinence.

Although it is possible that the alleged improved mental condition[1] may have been due to mental suggestion (p. 243), still the fact remains that it has been proved by Chittenden's work that the allowance of proteid necessary for continued health and

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[1] Chittenden: *Loc. cit.*, p. 51.

strength may be reduced during many months to half or less of what the habit of the appetite suggests.

It remains to be seen whether this quantity of proteid in the ration, which is not greater than the body would metabolize in starvation, is advisable as a program for the whole of one's adult life.

The foods with the strongest flavors are meats, which therefore add relish to a repast, and stimulate the digestive secretions.

Chittenden believes that the large quantity of proteid in an ordinary diet is due to self-indulgence. He protests against such indulgence, and thinks that a needless strain is thereby imposed upon the liver, kidneys, and other organs concerned in the transformation and elimination of the end-products of proteid metabolism.

Lichtenfelt,[1] on the other hand, shows that while there is no statistical difference in the height of individuals as due to occupation, still the people of Southern Italy are not so large nor so well developed physically as their fellows of Northern Italy. He explains this stunted growth as due to a low proteid and calorific intake in the food.

Hirschfeld [2] finds that the actual ration of a German soldier contains 98 grams of proteid, with no untoward results. He states that writers on economics, who believe the German populace underfed because they do not have 118 grams of proteid daily, are unduly pessimistic.

Although, as has been stated, the battle-ground has been over the allowance of 118 grams in Voit's dietary, it will be surprising to many to learn that Voit himself has said little on the subject. He[3] has shown that a vegetarian can live in nitrogenous equilibrium on a diet containing 48.5 grams of proteid and that an active working man weighing 74 kilos may get along on less than 118 grams. He discourages the tendency to eat meat in excess. He also discourages the practice of vegetarians

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[1] Lichtenfelt: "Pflüger's Archiv," 1905, Bd. cvii, p. 57.

[2] Hirschfeld: "Archiv für Physiologie," 1900, p. 380.

[3] Voit: "Zeitschrift für Biologie," 1889, Bd. xxv, p. 278.

who overload the digestive tract with the coarser kinds of vegetable foods which leave large indigestible residues.

It is not to be denied that 50 grams of proteid (containing 8 grams of nitrogen) are apparently able to maintain the adult body machine in perfect repair. Vegetarians, fruitarians[1] (who live on fruit and nuts) and vigorous adults who largely exclude proteid from the diet, are evidently able to live in health and strength upon this quantity. It must be, however, that more than this amount is advisable during growth or convalescence from wasting disease, or during the muscular hypertrophy which accompanies preliminary training for athletic effort.

Abderhalden[2] mentions the fact that whereas various body tissues are constructed of different proteids, so a large variety of amino acids must be available for their proper replenishment. Hence, it is reasonable to assume that a considerable excess of food proteid is essential to supply the special amino products for the synthesis of the characteristic proteids of the blood serum and those of the different organs.

It is certain that large ingestion of proteid in hot weather increases the heat production with accompanying increase in perspiration (p. 131). Meat should therefore be avoided in hot weather. In cold weather such an extra heat production may produce a pleasurable sensation of warmth. Dr. Folin, in personal conversation with the writer, said that a dietary of carbohydrates, fat and low proteid, was easily borne by a coachman during the summer, but during the winter the man complained of his sensitiveness to cold when taking the same diet.

Ranke[3] describes experiments on himself (weight = 73 kilograms) during the hottest months of summer weather in Munich, at which time he partook of an ample diet, rich in proteid (135 grams), containing 3300 calories,—a diet which he

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[1] Jaffe: U. S. Department of Agriculture, Bulletin No. 132.

[2] Abderhalden: "Zentralblatt für d. ges. Physiol. und Path. d. Stoffwechsels," 1906, Bd. i, p. 225.

[3] Ranke: "Zeitschrift für Biologie," 1900, Bd. 40. p. 299.

had enjoyed during the preceding winter. He had to force himself to eat. He was first attacked by catarrh of the stomach, from which he recovered by dieting, and subsequently became infected by diphtheria. He had formerly suffered from catarrh of the stomach while residing in the tropics. The excess of food, and especially of proteid, threw an unnecessary burden upon the heat-regulating apparatus which would not have taken place had the dictates of the appetite been allowed full sway and had the ration voluntarily been reduced.

From the knowledge at hand there appears to be no strongly substantiated argument why that portion of mankind living in a cool climate should not follow the general custom of taking a medium amount of proteid in moderate accordance with the dictates of their appetites. Everyone knows that excessive ingestion of highly flavored meats results in jaded appetite, an automatic signal of excess.

A similar excess of food when given to dogs results in vomiting. Rubner[1] says that many years of experience with dogs leads him to believe that appetite and capacity for digestion and absorption depend on the dog's requirement for energy in his given state of nutrition. A diet which a dog will greedily devour when in a room at a temperature of 0°, he will in part refuse when at a temperature of 33°.

While the proteid quantity in the diet may vary within wide limits with the taste, the purse, or the fad of the individual, the quantity of calorific energy required by the organism is a remarkably constant factor, being 35 calories per kilogram of body weight in the average man doing light work on a mixed diet. Comparatively little of this energy is furnished by proteid.

In a fasting individual, proteid furnishes 13 and fat 87 per cent. of the total heat given off from the body.

In Voit's medium mixed diet designed for a laboring man, the 118 grams of proteid furnishes about 15 per cent. of the total of 3055 calories.

In such an experiment as Siven's, mentioned on page 178,

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[1] Rubner: "Energiegesetze," 1902, p. 83.

which represents the lowest possible level of nitrogen equilibrium, the 25 grams of proteid ingested furnished 100 calories out of 2717 ingested in the food, or 3.6 per cent. However, since the total metabolism was measured as 2082 calories, the proteid furnished approximately 5 per cent. of this energy.

Chittenden[1] gives a dietary containing 50 grams of proteid and 2500 calories as sufficient for a soldier at work. This allows 8 per cent. of the total energy in proteid. These data may be thus summarized:

	Grams of Proteid in Diet.	Cal. from Proteid Metabolism in per cent.	Cal. from Fat and Carbohydrate Metabolism in per cent.
Starvation	0	13	87
Voit's standard (liberal proteid)	118	15	85
Chittenden's standard (reduced proteid)	50	8	92
Siven's minimum	25	5	95

The calories other than those contained in proteid may be given as carbohydrates or as fat. Voit allows a laborer 500 grams of starch (2050 calories) as the quantity which the intestinal canal may readily digest, and adds 56 grams of fat (521 calories) to the diet.

It has already been observed that half the calories may be given as fat and half as carbohydrates without affecting the carbohydrate power of economy over the proteid metabolism (p. 157).

This part of the subject really becomes a mere matter of calculation of the requirement of the resting organism, and the addition thereto of sufficient energy to accomplish the mechanical work.

How this is done has already been set forth in another chapter. A bicyclist riding for sixteen hours may have a metabolism amounting to 9000 calories daily, and the average ration of a Maine lumberman may rise to a value of 8000 calories. Champion wrestlers in a world's contest[2] may ingest daily during their

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[1] Chittenden: *Loc. cit.*, p. 254.

[2] Lavonius: "Skan. Archiv für Physiologie," 1905, Bd. xvii, p. 196.

periods of effort diets containing proteid 217.9 grams (35.1 grams of N); fat, 259.5 grams; carbohydrates, 431 grams; together, 5070 calories: or proteid, 182.2 grams (29.2 grams N); fat, 204.6 grams; carbohydrates, 392.3 grams; together, 4254 calories. Much cream was taken by these last-named individuals.

Chittenden[1] has fallen into error in the commendation of 2500 to 2600 calories as an ample diet for a solider at drill. For himself, pursuing a sedentary life, Chittenden prescribes 2000 calories or 35 per kilogram, while Mendel requires 2448 calories, or 35.3 calories per kilogram. These are entirely normal values for people at light work. In the earliest calculations of Voit, in 1866, it was shown that a man of 70 kilograms on a medium mixed diet, produced 2400 calories, or 34.3 calories per kilogram; and Rubner allows 2445 calories to men of 70 kilograms weight engaged in occupations involving light muscular work,—such men as writers, draughtsmen, tailors, physicians, etc. But the soldiers under Chittenden were put for two hours in the gymnasium, then apparently drilled for one hour, and walked another hour. This physical work requires increased energy from metabolism. It has been shown that to walk 2.7 miles in an hour on a level road requires an increased metabolism of 159.2 calories in a man weighing 70 kilograms. If a soldier during four hours actually expended this equivalent mechanical energy in excess of the amount of Professor Mendel in his laboratory, then his metabolism would be larger than Professor Mendel's by 637 calories, or he would have a total metabolism of 3085.

In Chittenden's experiments there was no analysis of the expired air, and conclusions are drawn from the maintenance of body weight.

Several of the larger sized soldiers (those who weighed 70 kilograms) lost between 3.5 and 8.5 kilograms of body weight during the experiments. Fritz, weighing 76.0 kilograms, lost 3.6 kilograms in five months. Had this all been fat, one can estimate that its heat value would have been 33,480 calories,

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[1] Chittenden: *Loc. cit.*, p. 254.

or an available daily combustion of body substance equal to 223 calories. Conclusions drawn from weight alone can be of only the roughest character (see p. 67).

For ordinary laborers working eight to ten hours a day—such as mechanics, porters, joiners, soldiers in garrison, and farmers—3000 calories does not seem an excessive quantity.

Rubner's diet calls for 2868 calories. Chittenden's allowance (2500-2600) is too low, while Atwater's (3400) appears excessive.

A third class are men at hard labor, such as soldiers in the field, shoemakers, blacksmiths, etc. For these Voit allows a dietary containing 3574 calories; Rubner 3362 calories; and Atwater 4150 calories. The differences in these figures are merely differences in the quantity of work alone.

In almost all the rations given, carbohydrates do not exceed 500 grams. The remainder is made up of fat.

Woods and Mansfield[1] report a dietary study of a camp of fifty Maine lumbermen actively engaged in chopping and yarding logs. The investigation continued for six days. The daily average ration per man was as follows: Proteid, 164.1 grams; fat, 387.8 grams, carbohydrates, 982.0 grams; calories, 8083.0. This dietary would appear almost fabulous were it not for the fact that Atwater has actually shown that a metabolism equivalent to 9300 calories a day may be produced by a man riding a stationary bicycle for sixteen hours.

A lower ration than the lowest here mentioned may be allowed to one who is confined to his bed (p. 74). In many hospitals, however, it has been found that liberal feeding of the very poor is often better than medicine.

The "standard" dietaries are given below, not because they are inflexible requirements in any sense of the word, but merely for the convenience of the reader. The individual standard will ever be controlled by climate, the amount and kind of mechanical effort; by appetite, purse and dietetic prejudice.

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[1] Woods and Mansfield: *Loc. cit.*

STANDARD DIETARIES FOR A MAN OF 70 KILOGRAMS.

	Voit.	Rubner.	Atwater.
Light work:			
Proteid	..	123	100
Fat	..	46	*
Carbohydrates	..	377	*
Calories	..	2445	2700
Medium work:			
Proteid	118	127	125
Fat	56	52	*
Carbohydrates	500	509	*
Calories	3055	2868	3400
Hard work:			
Proteid	145	165	150
Fat	100	70	*
Carbohydrates	500	565	*
Calories	3574	3362	4150

*Carbohydrates and fats to make up the fuel value.

Rubner[1] cites the following food values consumed daily per inhabitant of different cities, based upon municipal statistics of gross consumption:

MUNICIPAL FOOD STATISTICS.

	Proteid.	Fat.	Carbohydrates.	Calories.
Königsberg	84	31	414	2394
Munich	96	65	492	3014
Paris	98	64	465	2903
London	98	60	416	2665

In contrast to this comparative uniformity hospital dietaries, as regulated by the management of such institutions, vary greatly. Rubner[2] cites the following hospital dietaries:

HOSPITAL DIETARIES.

	Proteid.	Fat.	Carbohydrates.	Calories.
Munich	92	54	157	1381
Augsburg	94	57	222	1823
Halle	92	30	393	2267
England	107	69	533	3266

It is evident that the population of a city will sustain itself

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[1] Rubner: Von Leyden's "Handbuch der Ernährung," 1903, Bd. i, p. 160.

[2] Rubner: *Loc. cit.*, p. 157.

in accordance with its needs. In public institutions, however, such as poorhouses, prisons, asylums, hospitals, and in military and naval establishments, scientific knowledge of the needs of the individual becomes a very important consideration. The prolonged endurance of an army of soldiers is just as dependent on an ample army ration as is the battleship dependent on its supply of fuel. Not only the quantity of the food makes for the well-being, but it must taste well. No amount of actual fuel value could compel the American soldiers of the Spanish-American war to eat the "embalmed beef" furnished by the Government. The flavor is to the man what oil is to the machinery of the battleship. Without flavor in the food the digestive apparatus does not run smoothly. In ordinary civilized life even psychical influences act. The cloth on the table must be spotless, and the environment inviting.

One takes as food milk, eggs, various meats, such as beef, veal, pork, mutton, fish; also cereals, such as bread, rice, corn, macaroni, beans, and peas. Sometimes alcoholic beverages are added.

The calorific values of the various nutrient materials may be calculated by determining the composition of the latter by analysis and by multiplying the number of grams of each constituent by the factor which represents its fuel value to the organism (p. 40).

As a simple illustration of this the following experiment of Rubner[1] may be cited. A man weighing 46 kilograms ate nothing but eggs for two days,—22 on the first day and 20 on the second. The 22 eggs contained 1017.4 grams of material; the 20, 878.8 grams; an average of 948.1 grams per day. Since 100 grams of egg contain 14.1 grams of proteid and 10.9 grams of fat, 948.1 grams would contain a daily allowance of 133.6 grams of proteid and 103 grams of fat. If Rubner's standard values for the energy content are used, the result will be as follows:

133.6 grams proteid × 4.1 = 547 calories.
103.3 grams fat × 9.3 = 967 calories.

Total.............. = 1514 calories.
or 33 calories per kilogram.

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[1] Rubner: "Zeitschrift für Biologie," 1879, Bd. xv, p. 127.

This dietary of eggs was therefore nearly sufficient for the fuel requirement of this undersized individual. Notwithstanding the large amount of proteid in the dietary, there was a loss of body proteid equal to 7.5 grams per day.

The results of an exclusive milk diet are thus summarized by Rubner:[1] Milk (2438 grams) containing 84 grams of proteid and two-thirds of the requirement of energy for the individual, produced a deposit of proteid equal to 6.7 grams daily (p. 158). To cover a requirement of 2400 calories daily 3410 grams of milk would be needed, which contain 140 grams of proteid. For a laboring man with a requirement of 3080 calories, 4380 grams of milk with 180 grams of proteid would be necessary.

It is evident that milk with its high proteid content is a food *par excellence* for the growing organism or for the invalid convalescing from wasting disease. It contains too large an amount of proteid for a normal adult. A mixture of milk, toast and cream (creamed milk-toast) may produce a "modified milk" of proper value and easy digestibility.

Rubner finds that 1500 grams of good white bread containing 104.4 grams of proteid (= 75.2 grams pure proteid) will maintain a workingman in nitrogenous and calorific equilibrium.

Atwater and Benedict[2] have conclusively shown that alcohol may be used in the economy in place of isodynamic quantities of carbohydrates and fats. They employed diets containing about 2500 calories for a man at rest and 3500 for a man at work. During the alcohol days 500 of the calories were supplied in the form of 72 grams of alcohol, or about what is contained in a bottle of claret. The metabolism of the individual as expressed in calories was unchanged by the addition of alcohol to the diet. The alcohol was given in six small doses and 98 per cent. was burned by the organism.

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[1] Rubner: Von Leyden's "Handbuch der Ernährungstherapie," 1903, Bd. i, p. 132.

[2] Atwater and Benedict: "Memoirs of the National Academy of Sciences," Washington, 1902, vol. viii, p. 231.

The following table shows the average of experiments on a resting individual which lasted 23 days:

INFLUENCE OF ALCOHOL ON METABOLISM.

	Duration in Days.	In the Food in Grams.			Alcohol.	Cal. in Food.	Cal. of Metabolism.	Proteid Balance.
		Proteid.	Fat.	Carbohydrates.				
Ordinary diet ...	13	114	69	354		2496	2221	—2.0
Alcohol containing diet,	10	115	47	273	72.2	2488	2221	—3.8

On the ordinary diet 33.7 grams of fat were daily added to the body, and on the alcohol days 34.1 grams. These very valuable observations make it evident that alcohol is not a direct cause of obesity. If, however, a young man having acquired certain dietary habits at home, continues the same dietary at college and begins to drink "in moderation" besides, his increasing rotundity as he returns on his vacations can be readily explained by the sparing influence of alcohol upon the fat in his diet.

A liter of German beer contains 3 to 4 per cent. of alcohol and 5 to 6 per cent. extractives. It yields 450 calories to the body, only half being derived from alcohol, the rest from the dextrin and proteid-like extractives. Here is a material whose "fattening" properties may be very highly considered.

All alcoholic beverages are taken with a twofold object,—first, the desire for flavor, and second, for stimulation. Their food value, as above described, is usually little considered. In general it may be said that alcohol as a stomachic is valueless when the gastric juice is normal, but is beneficial in cases of hypersecretion, hypoacidity, and loss of appetite. Under these circumstances small amounts of beverages containing 5 to 10 per cent. of alcohol are sufficient for all purposes.[1]

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[1] Zitowitsch: Abstract in "Biochem. Centralblatt," 1905, Bd. iv, p. 574.

The subject of alcohol could be spun out into a considerable story, but for further details the reader is referred to other sources.[1]

To arrange a proper dietary for a given individual or group of individuals the very complete and valuable tables of Atwater will be found most practical. They are added in an appendix at the end of this volume for the benefit of the student who may desire to apply in practice his knowledge of the general laws of metabolism.

Underfed or overfed individuals may alike become objects of commiseration and proper subjects for rehabilitation.

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[1] The Use of Alcohol in Medicine: F. G. Benedict, A. R. Cushney, S. J. Meltzer, Graham Lusk, "Boston Medical and Surgical Journal," 1902, vol. cxlvii, p. 31.

CHAPTER X.

THE FOOD REQUIREMENT DURING THE PERIOD OF GROWTH.

In the last chapter the average food requirement of a normal adult organism was discussed. This diet, however, may be exceeded in cases where there is a renewal of tissue following wasting disease, or where there exists a development of new tissue, as during pregnancy, or afterwards during lactation, which involves the growth of the new-born infant.

Tangl[1] has reported some interesting observations on the heat production which takes place in the hen's egg incubated at 38°–39°. Tangl called this the "energy for development" or the "ontogenetic energy." His method was to determine the calories in fresh laid eggs and to compare that amount with the calories found within the egg-shell at the moment of the birth of the chick. In this latter case the chick and the balance of egg-yolk were determined separately.

The results of these experiments showed that for the development of one gram of chick 658 small calories were used, or for the production of one gram of solids contained in a new-born chick 3425 small calories were required.

Farkas[2] has since shown that for the development from the egg of one gram of silkworm larvæ 882 small calories are required, or for one gram of dry solids, 3125 small calories, figures which he compares with Tangl's for the egg.

When the whole hen's egg is considered, Tangl finds that 32 calories or 35 per cent. of the amount of chemical energy in the original egg is deposited in the body of the young embryo. Sixteen calories or 17 per cent. of the original total is used as the energy of development in the production of the young chick.

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[1] Tangl: "Pflüger's Archiv," 1903, Bd. xcviii, p. 327.

[2] Farkas: *Ibid.*, Bd. xcviii, p. 490.

The balance or 48 per cent. of the original energy in the egg is largely found in the abdomen of the chick and is absorbed by the animal during the early days of life.

It is apparent from the above that approximately one-sixth of the energy in a hen's egg is used in the development of a chick whose body contains one-third the original energy of the egg. The other half of the energy becomes available for the chick during the first days of his life, through absorption from the intestinal wall.

Tangl finds that each egg loses in solids during incubation, and that the heat value of one gram of such solids is over 9 calories. Since one gram of fat yields 9.3 calories, the natural inference is that fat furnishes the energy for development.

Hasselbalch[1] had formerly shown that the respiration carried on by an egg indicated a respiratory quotient $\left(\frac{CO_2}{O_2}\right)$ amounting to 0.677. This low quotient points to the combustion of fat.

It is obvious from this work that chemical energy derived principally from the oxidation of fat is used in the development of the embryonic chick—the energy of ontogenesis. So, during pregnancy in the higher animals, not only must there be growth of the breasts, the uterine musculature, and growth of the embryo itself, but there must be energy expended in maintaining the new organism. Hence the appetite of the mother increases during pregnancy. Magnus-Levy[2] finds an increased requirement for oxygen on the part of the mother as pregnancy progresses. His table is as follows:

			Oxygen in c.c. per min.
Non-pregnant			302
Third month of pregnancy			320
Fourth	"	"	325
Fifth	"	"	340
Sixth	"	"	349
Seventh	"	"	378
Eighth	"	"	363
Ninth	"	"	383

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[1] Hasselbalch: "Skan. Archiv für Physiol.," 1900, Bd. x, p. 353.

[2] Magnus-Levy: "Zeitschrift für Gynäkologie u. Geburtshilfe," 1904, Bd. lii. Also see Magnus-Levy: Von Noorden's "Handbuch des Stoffwechsels," 1906, Bd. i, p. 409.

Magnus-Levy estimates that of the 80 c.c. additional oxygen required during the ninth month of pregnancy, only 10 c.c. are used for the metabolism of the fetus, 20 c.c. for the increased respiratory and heart activity, while 50 c.c. are for the general needs of the maternal organism, which has increased in size and weight.

On empirical grounds von Winckel[1] for many years has used the following diet for pregnant women with, he says, "excellent results":

Proteid	90 grams.	369 calories.
Fat	27 "	251 "
Carbohydrates	200 "	820 "
Total		1440 "

This certainly seems a very low ration and one hardly compatible with furnishing the full calorific requirement. The dietary provided in the New York Infirmary for Women and Children is twice as large, being Atwater's diet for a woman doing moderate work. It is as follows:

Proteid	100 grams.	410 calories.
Fat	100 "	930 "
Carbohydrates	360 "	1476 "
Total		2816

Not the mere maintenance of the mother, but a charitable contribution of reserve tissue for herself and offspring is here effected.

Some very instructive experiments have been performed to ascertain the course of the proteid metabolism before and after pregnancy.

Zacharjewski[2] investigated the nitrogen metabolism of nine pregnant women. In three primiparæ nourished on diets containing an average of 16.5 grams of nitrogen, there was an average daily retention of 1.4 grams in the mother's organism

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[1] Von Winckel: Von Leyden's "Handbuch der Ernährungstherapie," 1904, Bd. ii, p. 469.

[2] Zacharjewski: "Zeitschrift für Biologie," 1894, Bd. xxx, p. 405.

for thirteen days before parturition. In six multiparæ the diet contained 20.66 grams of nitrogen and there was a daily retention of 5.122 grams of nitrogen during the last eighteen days of pregnancy. The figures correspond to a considerable construction of proteid tissue within the organism. After childbirth there was always a loss of tissue nitrogen by the mother. In one case nitrogen equilibrium was established on the fifth day, and in another on the fourth. In six cases the loss of body nitrogen continued over a longer time. Zacharjewski says that the process of involution of the uterus is greatest during the first five to seven days after delivery, and the high nitrogen output from the mother is the result of this. After the elimination which is due to these regressive changes, there is a retention of nitrogen. This is probably attributable to the building up of the lactic glands, for Slemons[1] shows that nitrogen equilibrium, once established, was constantly maintained in a woman who did not nurse her child.

The complete record of the nitrogen elimination of a nursing mother, one of Slemons's cases, is here reproduced. It is especially instructive on account of the constancy of the quantity of nitrogen in the diet. The woman was a negress who gave birth to a healthy, vigorous child.

During the last days of pregnancy there was an average daily storage of 2.98 grams of nitrogen, and for eight days of the puerperium an average loss of 4.5 grams. Later, between the nineteenth and twenty-fifth days after birth there was an average daily storage of 2.52 grams of nitrogen. This may have been for the purpose of increasing the size of the breasts. It must be remembered that even during the period of involution an increase in the lactic glands may have been taking place at the expense of proteid derived from the uterus. So the debit balance of nitrogen during this period may not represent all the proteid change taking place.

The mother had plenty of milk and the baby gained an average of thirty grams a day during the first forty days of his life.

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[1] Slemons: "Johns Hopkins Hospital Reports," 1905, vol. xii p. 121.

Slemons remarks that the low proteid metabolism as indicated by the urinary nitrogen of the period of settled lactation is a proof that there can be no important production of milk fat from proteid.

PROTEID METABOLISM BEFORE AND AFTER CHILDBIRTH.

WEIGHTS ARE IN GRAMS.

DAYS BEFORE AND AFTER DELIVERY.	N IN FOOD.	N IN URINE.	N IN FECES.	N IN MILK.	N IN LOCHIA.	N BALANCE.
11	20.5	11.9	0.53	..	..	+8.12
10	19.2	16.6		..	..	+2.07
9	18.	10.9		..	..	+6.57
8	16.9	17.1		..	..	—0.77
7	11.3	13.7		..	..	—2.95
6	19.2	13.3		..	..	+5.39
5	19.2	12.1		..	..	+6.57
4	19.2	14.1		..	..	+4.54
3	18.0	12.3		..	..	+5.12
2	14.9	12.3		..	..	+2.06
1	8.0	11.5		..	..	—4.00
Delivery	4.2	8.4		..	3.15	..
1	7.1	13.3	1.14	..	2.31	—9.66
2	13.7	13.2		0.15	1.99	—2.79
3	19.	15.8		1.04	1.61	—0.57
4	19.	18.8		1.99	1.19	—4.13
5	20.	15.6		2.02	1.05	+0.15
6	20.	21.8		2.15	1.4	—6.5
7	19.	18.1		2.02	0.84	—3.14
8	11.	16.8		2.02	0.28	—9.2
19	19.8	12.1	1.6	1.18	..	+4.89
20	18.8	15.3		1.29	..	+0.57
21	19.9	13.3		1.57	..	+3.39
22	17.3	9.7		1.58	..	+4.39
23	18.3	13.9		1.85	..	+0.68
24	18.75	11.4		2.03	..	+3.72
25	19.	15.6		1.58	..	—0.16

In the above experiment it will be noticed that the nitrogen of the milk is small in quantity as compared with the urinary nitrogen. On a strictly vegetarian diet the relation would change. Thus Voit[1] found 48.8 grams of nitrogen in the milk of a cow and 93.7 grams of nitrogen in her urine for the same period. Fingerling[2] finds 5.97 grams of nitrogen in the milk of a goat and in her urine 9.48.

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[1] Voit: "Zeitschrift für Biologie," 1869, Bd. v, p. 122.

[2] Fingerling: *Ibid.*, 1905, Bd. xlvii, p. 84.

The influence of nutrition on the production of milk has been the object of countless investigations, but unfortunately most of these experiments have been conducted for commercial purposes on cows and goats. These animals, with their fundamental ration consisting of hay, do not allow of the ingestion of simple foods. On the other hand the milk supply of even a large bitch is very limited in quantity and is with difficulty obtained. The writer is not aware of any systematic observations on the composition of human milk as influenced by food, although such researches would seem of vast importance.

Perhaps the most valuable research which can to-day be used is an old one of Voit[1] upon a bitch weighing 34 kilograms. It confirmed the previous work of Kemmerich and of Subotin. The animal was given meat alone, meat and starch, meat and fat, starch alone, fat alone, and was also starved. The influence upon the milk secretion was found to be comparatively small. The research is a model of completeness, the plan of which could well be copied in an experiment on a human being.

A part of the results are given below:

INFLUENCE OF DIET ON THE COMPOSITION OF THE MILK OF A DOG WEIGHING 34 KILOGRAMS.

Food.				Milk.						
Day.	Meat in Grams.	Other Food in Grams.	N in Grams.	Amount in c.c.	N in Grams.	Fat in Grams.	Sugar in Grams.	Proteid in Per Cent.	Fat in Per Cent.	Sugar in Per Cent.
6.	1000	300 starch	34.	115	1.1	8.8	3.1	9.9	7.70	2.71
7.	1000	200 fat	34.	144	1.4	10.8	3.8	9.9	7.50	2.67
8.	1000	200 fat	34.	135	1.1	11.3	2.9	7.4	8.39	2.15
9.	Mixed diet	. .	. .	151	1.4	13.9	3.4	9.6	9.22	2.24
10.	500	400 starch	17.	138	1.2	11.3	3.8	8.0	8.19	2.78
11.	500	300 fat	17.	168	1.6	16.5	4.2	10.1	9.83	2.52
12.	Starv.	. .	. .	149	1.5	13.8	3.9	9.5	9.24	2.65
13.	Starv.	. .	. .	118	1.0	12.2	3.0	6.7	10.32	2.58
14.	. .	500 starch	. .	137	1.1	10.1	4.3	7.4	7.39	3.11
16.	2000	. .	68.	158	1.6	16.1	4.4	10.6	10.17	2.82
17.	2000	. .	68.	161	1.7	14.7	4.7	10.9	9.11	2.91

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[1] Voit: "Zeitschrift für Biologie," 1869, Bd. v, p. 137.

The largest quantity of milk as well as the richest in proteid was obtained when meat or meat and fat were ingested. Curiously enough a diet of 500 grams of meat and 300 grams of fat gave milk of the same amount and quality as with 2000 grams of meat. It is usually said that a large proteid diet stimulates the milk secretion; but this may also be due indirectly to the multiplication of the gland cells.

The milk sugar content was scarcely affected by the diet, although a slight percentage increase was observed after starch ingestion.

The fat content was increased in starvation to its highest percentage. It was not very greatly affected by adding fat to a meat diet and it was greatly reduced by giving carbohydrates.

The action of fasting on the fat content of milk is better shown in the herbivorous goat. The writer[1] gave a milch goat a constant diet of hay, cornmeal and bran, starved the animal for two days, and then continued the former diet. The fat content of the milk was determined. The results were as follows:

Milk in c.c.	Fat in G.	Fat in per Cent.	
460	26.50	5.76	
470	25.90	5.52	
338	23.90	6.23	Starvation.
198	18.35	9.27	
232	18.75	8.08	
298	16.30	5.47	
348	19.40	5.61	
362	22.30	6.16	
490	27.70	5.66	

In fasting, therefore, the fat content in the milk of the herbivorous goat approaches that contained in the carnivorous dog. With a return to the normal diet the fat content in goat's milk is reduced to its former level.

Morgen, Beger and Fingerling[2] find that a diet rich in carbohydrate and poor in fat produces a poor cow's milk containing little fat, although the general condition of the animal remains

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[1] Lusk: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 42.

[2] Morgen, Beger and Fingerling: "Landw. Versuchsstationen," 1904, Bd. lxi, p. 1.

perfect. Addition of proteid increases the quantity of the milk without changing the low fat percentage. Replacement of some of the carbohydrate with isodynamic quantities of fat, up to 0.5 to 1.0 gram per kilogram of animal, largely increased the fat content of the milk and thereby its nutritive value.

It has long been known that ingested fat may appear in the milk of an animal. Quite recently Gogitidse[1] has shown that after giving linseed oil to sheep their milk fat may contain 33 per cent. of linseed fat. He also finds[2] that the fat of linseed oil passes readily into human milk, and that the fat of hempseed, while influencing the composition of the milk, greatly depresses lactation during the period of its ingestion.

How may these various effects of diet be explained? The subject requires a knowledge of the processes going on in the lactic gland and these are not certainly known. It has been generally believed that the cells of the lactic glands undergo a fatty metamorphosis and, themselves breaking up, pass into the milk (Voit, Heidenhain). The milk under these circumstances might be regarded as the substance of an organ, made fluid.

Schäfer,[3] however, believes the process to be one of secretion similar to that in the salivary glands, where the cells prepare the special constituents and pass them on to the lumen. Thus casein, like ptyalin, may be specially elaborated within gland cells.

If this be the true explanation, the influence of food, in the writer's opinion, may be readily explained. An increased proteid ingestion furnishes the digestive products of this substance in liberal quantities and may increase the activity of the gland.

The milk sugar content of the milk remains remarkably constant. Cremer,[4] for example, has shown that the percentage of milk sugar in the milk is unchanged in the cow after dimin-

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[1] Gogitidse: "Zeitschrift für Biologie," 1904, Bd. xlv, p. 365.

[2] Gogitidse: *Ibid.*, 1905, Bd. xlvi, p. 403.

[3] Schäfer: "Text-book of Physiology," 1898, vol. i, p. 667.

[4] Cremer: "Zeitschrift für Biologie," 1898, Bd. xxxvii, p. 78.

ishing the sugar content of the animal by inducing phlorhizin diabetes.

To explain the fat content of the milk, the writer offers the following theory: When for any reason sufficient sugar does not burn in the body cells, these sugar-hungry cells attract fat. It has already been seen that glycogen and fat content of the liver are mutually antagonistic. Before lactation sets in, the cells of the mammary glands burn sugar and there is no great attraction for fat. Milk sugar cannot be formed in any great quantity before parturition, because it occurs in the urine only *post-partum*.[1] But when in the process of lactation the dextrose furnished by the blood is converted into milk sugar (which cannot be burned within the organism), the lactic cell becomes a sugar-hungry cell which at once attracts fat from the blood. This theory of the writer explains the production of milk fat by the process of infiltration. The variation of the percentage of fat in the milk may be explained by the quantity of fat in the blood. During starvation the blood becomes rich in fat on account of the transportation of tissue fat to the cells. Administration of sugar at once reduces the supply of fat in the blood. But if fat be ingested with carbohydrates the blood becomes rich with this fat and affords material for a rich milk.

Administration of good cream with a substantial mixed diet is highly to be recommended for nursing mothers. The daily production of a liter of milk, which has a value of 640 calories, indicates the necessity of no small addition to the daily ration, if the woman is to bear satisfactorily the strain of lactation. Probably this extra nourishment is best given in the form of fat. Beer is also said to increase the fat content of the milk.[2]

Should the fat of the milk disagree with the infant, the trouble may be due to the kind of fat ingested by the mother. If, however, the indigestion be due to a large percentage of fat, a carbohydrate diet will reduce the percentage in the milk.

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[1] Lemaire: "Zeitschrift für physiologische Chemie," 1896, Bd. xxi, p. 442.

[2] Temesvary: "Centralblatt für die med. Wissenschaften," 1900, Bd. xxxviii, p. 688.

A very important fact regarding the nutrition of the young is that the milk of one race is specifically adapted to the growth of the offspring of that particular race. Bunge[1] found that dog's milk had an ash of exactly the same composition as the ash of the new-born puppy. The ash of the milk was therefore perfectly adapted for the construction of new puppy tissue. It was, however, entirely different in composition from human, or cow's, or other milk. Only in the case of iron is the quantity lower than corresponds to the composition of the offspring, but this factor is offset by the fact that the animal when new-born is richer in iron than it is at any other period of life. Not only this, but the casein of the different milks is different in chemical behavior. And besides this, the rennin of the stomach is said to be specifically adapted for the coagulation of the casein produced by the female of the same race.[2]

Furthermore, the percentage quantity of the constituents in the milk is dependant upon the rapidity of the growth of the organism. Bunge[3] has shown this in the following comparative table:

	Time in Days for the New-born Animal to Double its Weight.	100 Parts of Milk Contain		
		Proteid.	Ash.	Calcium Oxide.
Man	180	1.6	0.2	0.0328
Horse	60	2.0	0.4	0.124
Calf	47	3.5	0.7	0.160
Kid	19	4.3	0.8	0.210
Pig	18	5.6	..	....
Lamb	10	6.5	0.9	0.272
Dog	8	7.1	1.3	0.453
Cat	7	9.5	..	....

Camerer[4] finds that human milk, drawn three to twelve days after parturition, contains 0.2 milligram of iron (Fe_2O_3) per 100 c.c., while the later milk contains 0.1 milligram. The quantity is decreased if the environment or the condition of the

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[1] Bunge: "Zeitschrift für Biologie," 1874, Bd. x, p. 326.

[2] Kiesel: "Pflüger's Archiv," 1905, Bd. cviii, p. 343.

[3] Bunge: "Lehrbuch der physiologische Chemie," 1898, p. 118.

[4] Camerer: "Zeitschrift für Biologie," 1905. Bd. xlvi, p. 371.

mother be poor.[1] Using the customary methods of infant feeding with cow's milk, the infant obtains too little iron.

Blauberg[2] reports the following percentage absorption of the ash of cow's and human milk:

Kind of Milk.	Subject.	Per Cent. Milk Ash Absorbed.
Cow's	Infant.	60.70
Diluted cow's	"	53.72
Human	"	79.42
Human	"	81.82
Cow's	Adult.	53.20

The quantity of calcium in cow's milk is in excess of the needs of the human infant.

The absorption of the energy-containing constituents of the milk is remarkably constant. This is illustrated in the following table made from Rubner's experiments[3] which show the physiological utilization of the total calories of milk:

	Per Cent. of Calories Absorbed.
Human milk	91.6 to 94.0
Diluted cow's milk	90.7
Diluted cow's milk + milk sugar	92.2
Same given to stunted infant	87.1
Cow's milk given to an adult	89.8

As regards the relative composition of average cow's and human milk five and a half months after parturition, the following comparison may be made.

PERCENTAGE COMPOSITION OF COW'S AND HUMAN MILK.

	Cow's.[4]	Human.[5]
Proteid	3.41	1.0
Fat	3.65	3.0
Milk sugar	4.81	6.4

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[1] Jolles and Friedjung: "Arch. für experimentelle Path. und Pharm.," 1901, Bd. xlvi, p. 247.

[2] Blauberg: "Zeitschrift für Biologie," 1900, Bd. xl, p. 44.

[3] Rubner: *Ibid.*, 1899, Bd. xxxviii, p. 380. For further statistics of absorption consult Tangl: "Pflüger's Archiv," 1904, Bd. civ, p. 453.

[4] Rubner: Von Leyden's "Handbuch," 1903, Bd. i, p. 95.

[5] Rubner and Heubner: "Zeitschrift für ex. Pathologie und Therapie," 1905, Bd. i, p. 1.

Or, expressed in the relative calorific value of the different constituents this comparison may be given:[1]

PERCENTAGE DISTRIBUTION OF CALORIES IN COW'S AND HUMAN MILK.

	Cow's.	Human.
Proteid	21.3	7.4
Fat	49.8	43.9
Milk sugar	28.9	48.7

Here, then, there are tremendous differences of composition which forces the conclusion that cow's milk is not to be substituted for human milk in rearing a child.

Patein and Daval[2] find that human milk after the first month of lactation contains but 0.8 to 1 per cent. of casein.

Another distinction between cow's and human milk is that the former contains but little extractive nitrogen while the latter may contain 18 to 20 per cent.[3] This is probably one of the causes of the increase of the $\frac{C.}{N.}$ ratio (p. 36) to over one in the urine of breast-fed infants.

The large proteid content of cow's milk may be evil for the child. In the first place it clots in a heavy mass in the baby's stomach; and in the second place, even though it be digested, it is relatively much above the requirement of the organism, and its specific dynamic action increases the amount of heat produced.

If cow's milk be diluted with two or more parts of water, its proteid content may approach that of human milk and its precipitation by rennin in the stomach is in the form of flakes. This precipitation of cow's casein takes place in even finer flakes when the milk is mixed with barley water, as was shown by Chapin.

Chapin's observations, in which the writer assisted, have been confirmed by White,[4] who says that this action is due to the presence of three-fourths to one per cent. of dissolved starch.

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[1] Rubner: "Energiegesetze," 1902, p. 418.

[2] Patein and Daval: "Journal de Pharm. et de Chemie," 1905, T. 21, p. 193.

[3] Rubner and Heubner: *Loc. cit.*

[4] White: "Journal of the Boston Society of Medical Sciences," 1900, vol. v, p. 130.

The dilution of cow's milk, however, reduces the quantity of fat and carbohydrates, and these must therefore be added to the milk in order to make a proper diet for a child.

To obtain a sufficient fat content, "top milk," rich in fat, may be taken from milk which has been standing, and may be mixed with water. Milk sugar may then be added.

Such a milk is called "modified milk" and infants are brought up on it with greater success than was the case when undiluted cow's milk was given.

Human milk has a varying calorific value dependent largely on the amount of fat present. Thus Schlossmann[1] finds the calorific value per liter of nineteen samples of milk from nineteen women averages 719 calories, with a maximum of 876 and a minimum of 567. The milks having the largest fuel value contained 5.2 to 5.1 per cent. of fat, while that having the lowest contained only 1.8 per cent.

The amount of the child's metabolism is dependent on his size. Rubner states that a baby weighing 4 kilograms produces 422 calories, an adult weighing 40 kilograms, 2106 calories. But the metabolism per unit of area is the same.

Rubner and Heubner[2] summarize their results on the metabolism of differently conditioned children as follows:

	WEIGHT IN KG.	CALORIES PER SQ. METER OF SURFACE.
Infant of stunted growth	3	1090
" at the breast	5	1006
" on cow's milk	8	1143
" at the breast	10	1219

The metabolism in all these cases was essentially the same per unit of area.

In the last case the very noticeable amount of muscle movement and crying while the child was in the respiration appa-

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[1] Schlossmann: "Zeitschrift für physiologische Chemie," 1903, Bd. xxxvii, p. 340.

[2] Rubner and Heubner: "Zeitschrift für ex. Pathologie und Therapie," 1905, Bd. i, p. 1.

ratus increased the metabolism. Further details regarding this case give a very complete picture of the metabolism of an infant. The child weighed 4.06 kilograms at birth, and about 10 kilograms at the time of the experiment when five and a half months old. He was given his mother's milk.

The first day of the experiment the child was very uncomfortable on account of his new environment. The last day he was given only a small quantity of tea, and was therefore in a state of practical starvation. The carbon dioxid excretion on these days was as follows:

Day.	Grams of CO_2 in 24 Hours.
First	278.8
Second	219.9
Third	228.1
Fourth	231.1
Fifth	218.2

The diet on the second, third and fourth days consisted of 1258 grams of human milk per day containing:

Total nitrogen	1.99 grams.
Fat	37.73 "
Milk sugar	80.5 "

Of the total nitrogen only 1.63 grams were contained in true proteid, the rest being in nitrogenous extractives. The percentage composition of this milk is given on page 203. Its actual nutritive value was 634.5 calories.

The balance sheet of the respiration experiment showed the following daily result:

METABOLISM OF AN INFANT.

Day.	Food.	N in Food.	N in Urine.	N in Total Excreta.	N Balance.	C in Food.	C in Excreta.	C Balance.
		Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.
2, 3, 4.	Milk	1.99	1.13	1.53	+0.46	63.7	65.8	—2.1
5......	None	..	1.18	1.18	—1.18	..	60.8	—60.8

The infant was nearly in calorific equilibrium during the period of milk ingestion. There were 634.5 available calories in the milk and 660.5 calories produced in the metabolism.

The quantity of the proteid metabolism was extremely small, being 9.6 grams according to the usual method of computation. The milk contained proteid to the extent of 7 per cent. of its total calorific content. Of this only 5 per cent. was metabolized and 2 per cent. was added to the body. The metabolism of an infant may therefore be maintained on a diet in which 5 per cent. of the energy is supplied by proteid and 95 per cent. by fats and carbohydrates.

The specific dynamic action of the milk was almost negligible, the metabolism being approximately the same during the period of feeding as during that of starvation. Curiously enough, the proteid metabolism was the same on days of milk ingestion as in starvation.

This child gained normally in weight before and after the respiration experiment, but during that time, struggling and crying prevented fat addition to the otherwise well-developed normal infant.[1]

W. Camerer, Jr.,[2] shows that a breast-fed infant nine months old may ingest 480 calories in the milk, produce 420 calories in metabolism and add 60 calories to his body, or 15 per cent. of the energy content of the diet. In this case 40 per cent. of the proteid intake was added to the growing organism.

Rubner and Heubner[3] have reported a respiration experiment on a child seven and a half months old, nourished with modified cow's milk. The intake was 682.8 calories, the metabolism 593.2, leaving 89.6 calories or 12.2 per cent. for addition to the child's organism.

It is remarkable that a child's intuitive sense of appetite should determine the ingestion of nutriment necessary to cover

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[1] Heubner: "Jahrbuch für Kinderheilkunde," 1905, Bd. lxi, Heft 3.

[2] W. Camerer, Jr.: "Zeitschrift für Biologie," 1902, Bd. xliii, p. 1.

[3] Rubner and Heubner: "Zeitschrift für Biologie," 1899, Bd. xxxviii, p. 345.

the energy requirement of his organism, and a small addition for normal development. A reduction of 15 per cent. in the intake of food would bring his prosperous growth to a standstill.

Heubner[1] says that the average normal infant requires 100 calories per kilogram of body weight for normal nutrition during the first three months of his life; 90 calories during the second three months, and 80 and less thereafter. The energy content of the food should never sink below 70 calories per kilogram, which is about the maintenance minimum.

Oppenheimer[2] first called attention to the fact that the growth in grams of normal breast-fed children of the same age, may be nearly proportional to the quantity of milk ingested. Here the milk presumably had the same calorific value throughout the experiment although this could not be determined. The quantity of milk taken at each meal was found by weighing the infant before and after nursing. Oppenheimer's table is here reproduced:

GROWTH IN GRAMS FOR 1 KG. MILK.

Month.	Feer's Subject.	Oppenheimer's Subject.
I	33.8	95.0
II	191.2	201.1
III	120.3	138.5
IV	102.6	103.3
V	57.7	120.8

The proportion of growth to milk given was practically the same during the second, third, and fourth months of these children's lives.

That the growth of suckling pigs may be proportional to the calorific value of the milk has been shown by work accomplished by Dr. L. C. Sanford and Dr. Margaret B. Wilson[3] in the writer's laboratory. Newly born pigs of two litters were reared on skimmed cow's milk and on the same milk fortified with two and three per cent. of glucose or of milk sugar. The experiments were continued from fourteen to sixteen days. The results obtained in these experiments are thus tabulated:

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[1] Heubner: "Berliner klinische Wochenschrift," 1901, p. 449.

[2] Oppenheimer: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 147.

[3] Wilson: "American Journal of Physiology," 1902, vol. viii, p. 197.

GROWTH OF SUCKLING PIGS.

	Wilson.			Sanford and Lusk.		
	Skim.	Lactose.	Dextrose.	Skim.	Lactose.	Dextrose.
Weight in grams when born	1322	1295	1485	1000	1050	1152
Weight in grams when killed	2205	2435	2471	1246	1890	2000
Growth in grams	883	1140	986	264	838	848
Growth in per cent.	66.8	88.0	64.4	26.4	79.7	73.6
Milk fed in c.c.	10925	11005	9707	6826	8836	9481
Available calories fed	4053	5216	4620	2339	3736	3972
Growth in grams per liter of milk	81	114	101	38	95	89
Growth in grams per 1000 calories fed	218	215	213	114	222	213

It is seen that the growth of the pigs in grams was directly proportional to the calorific value of the food to the organism. The one exception was that of an ill-nourished pig fed with skimmed milk. This was an improperly nourished animal taking too little food and remaining behind his fellows in normal development. But that five out of six pigs of different litters, of different sizes and differently fed, should have gained in weight respectively 213, 214, 215, 218, and 222 grams per thousand calories in the food ingested seems more than a coincidence.

A pig doubles in weight in eighteen days after birth. The pig of Dr. Wilson, brought up on skimmed milk with 3 per cent. of milk sugar added, nearly doubled in weight in sixteen days.

Comparing the fuel value of sow's milk and that of the skimmed cow's milk to which milk sugar had been added, the following results are significant. Of 100 calories in the food there are:

	Sow's Milk.[1]	Skim Milk + 3 Per Cent. Milk Sugar.
Proteid	34.1	36.5
Fats	52.4	2.5
Carbohydrates	13.5	61.0

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[1] Calculated from König: "Zusammensetzung der menschlichen Nahrungsmittel," 1889, p. 350.

It is apparent from this that normal growth of the young organism may be attained by the replacement of fat by milk sugar in isodynamic quantity. This fact may become of importance in infant feeding.

Dr. Wilson found that when the pigs reared on these diets were killed and their composition compared with that of three pigs of the same litter which were killed at birth, there was a retention for growth of 18 to 19 per cent. of the energy in the food. This retention of a definite nutrient factor is a necessary corollary to the fact of the growth being proportional to the calorific intake.

In children Camerer found 15 per cent., Rubner and Heubner 12.2 per cent. so retained.

The percentage of calcium (CaO) in the dry solids of the pigs reared on the various skim milks was 8.29, 8.02 and 8.13, showing that the absorption of calcium depended on the growth of the organism, and not on a variation in the quantity ingested.

Another instance which demonstrates that the young organism may grow in proportion to the energy ingested in the food, is brought to light by calculations based on the work of E. Rost.[1] This author gave meat, fat and bone ash to three dogs of the same litter, the experiment starting on the ninety-eighth day of their lives and continuing eighty-eight days. The writer has thus calculated the results:

	Dog. I.	Dog. II.	Dog. III.
Weight in grams at start...	3,200	2,200	4,150
Weight in grams at end....	6,280	4,620	8,750
Growth in grams	3,080	2,440	4,600
Growth in per cent........	96	110	110
Available calories ingested.	24,420	17,336	34,276
Gain in grams per 1000 calories ingested...........	122	141	134

It is worthy of note that these growing dogs, fed with meat and fat, gained in weight nearly the same number of grams per 1000 calories ingested in the food. This law of growth seems reasonably established. It simply expresses the fact

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[1] Rost: "Arbeiten aus dem kaiserlichen Gesundheitsamte," 1901, Bd. xviii, p. 206.

that during the normal development of the young of the same age and species, a definite percentage of the food is retained for growth irrespective of the size of the individual.

Bunge[1] has recently recalled the relationship between rapidity of growth and longevity, as originally suggested by Flourens in 1856. This writer believed that if the time of reaching the end of growth be multiplied by five, the average term of life might be computed. This relationship may thus be tabulated:

TABLE SHOWING FLOURENS' LAW OF LONGEVITY.

	Time in Days from Birth to Double Birth-weight.	Time in Years Until Full Growth.	Deduced Average Longevity in Years.	Maximum Recorded Longevity in Years.
Man	180	20	90–100	152–169
Camel	..	8	40	100
Horse	60	5	25	50
Cow	47	4	15–20	..
Lion	..	4	20	60
Cat	9½	1½	9–10	20
Dog	9	2	10–12	24

Bunge calls attention to the fact that a horse more often lives to be forty than a man to be a hundred. Either the law is false, or man is a too early victim of an improper heredity or environment.

For metabolism in boyhood, see page 146.

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[1] Bunge: "Pflüger's Archiv," 1903, Bd. xcv, p. 606.

CHAPTER XI.

METABOLISM IN ANEMIA, AT HIGH ALTITUDES, IN MYXEDEMA AND IN EXOPHTHALMIC GOITER.

In man one-thirteenth part of the body weight is carried as blood to the lungs at least every minute and there exposed for a period of two seconds to the action of the alveolar air. The blood in the capillaries of the lungs may be estimated as a film 0.01 millimeter in thickness, and 150 square meters in area, or nearly a hundred times the area of the surface of the body. Zuntz estimates the combined thickness of the alveolar wall and capillary wall at 0.004 mm. This is the total distance separating the alveolar air from the blood. The gaseous exchange between the air and the blood is thus readily made possible. Complete deprivation of oxygen results in asphyxiation and death.

The question arises, Will there be any effect upon metabolism if the oxygen supply for the body be reduced? Such a reduction of oxygen available for the tissues might be brought about by bloodletting, anemia, carbon-monoxid poisoning, by life on high mountains, or in balloons at high altitudes, or in pneumatic cabinets at reduced pressure, or by the artificial restriction of the free influx of atmospheric air into the lungs. Any of these methods if carried beyond a certain point is known to produce death.

It was noted by Lavoisier and confirmed by Regnault and Reiset that the respiration of pure oxygen did not increase the metabolism. Liebig was convinced that atmospheric pressure was without influence, for it was evident to him that life at the sea-level was of the same character as on high mountains. In confirmation of these principles Zuntz[1] has recently shown that

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[1] Zuntz: "Archiv für Physiologie," 1903, Suppl., p. 492.

if air rich in oxygen be respired, there is an increased oxygen absorption lasting for about one minute, and then the normal quantity is absorbed. The primary increase in the quantity of oxygen absorbed is due to the filling of the lungs with oxygen and a further saturation of the blood with it, processes which are without effect on tissue metabolism. There is apparently no retention of such oxygen within the cells of the organism.

The consideration of the subject of subnormal oxygen supply may be taken up with bloodletting, which produces an artificial anemia. Bauer[1] in Voit's laboratory, was the first to study this systematically and found that the immediate result of bloodletting in the dog was an increased proteid metabolism, but that the carbon dioxid elimination was unchanged. Eighteen to 27 per cent. of the total blood in the body was removed in these experiments.

Hawk and Gies[2] confirm the results of a higher proteid metabolism after bloodletting.

Finkler[3] in Pflüger's laboratory withdrew one-third of the total blood from a dog, thereby reducing the rapidity of bloodflow in the femoral artery by one-half, and yet there was no change in the quantity of oxygen absorbed, and therefore of the quantity of the carbon dioxid exhaled. Finkler noted, however, that the quantity of oxygen in the venous blood grew constantly less after repeated bleedings. This indicates the inter-relation between the oxygen supply and the needs of the tissues. Under ordinary circumstances there are 20 volumes per cent. of oxygen in the arterial blood of which 12 volumes per cent. may return as an unused excess to the right heart. Repeated bleedings by Finkler reduced this percentage in venous blood from 11.80 per cent. to 8.80, 4.06, and 2.71 per cent. The carbon dioxid content of the blood remained unchanged. This decrease in the oxygen content of the blood may stimulate both the heart and respiration to compensatory activity, although nothing resembling

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[1] Bauer: "Zeitschrift für Biologie," 1872, Bd. viii, p. 567.

[2] Hawk and Gies: "American Journal of Physiology," 1904, vol. xi, p. 226.

[3] Finkler: "Pflüger's Archiv," 1875, Bd. x, p. 368.

asphyxia be present. While the total heat production is unchanged in anemia following bloodletting (except as influenced by increased cardiac and respiratory activity), still it is evident from the diminution of oxygen present in venous blood that a largely increased metabolism would not receive a sufficient supply of oxygen from the blood. Hence the anemic organism is incapable of great muscular work without quick exhaustion accompanied by rapid respiration and heart-beat. These latter are further efforts of compensation for the decrease in the oxygen-carrying elements of the blood.

Pettenkofer and Voit[1] observed the metabolism in an acute case of leukocythemia of four years' duration, and at a time four months before the death of the patient. There was one white to every three red blood-corpuscles, a high degree of anemia, and great physical weakness. The metabolism was exactly the same as in a normal resting man living under the same dietary conditions.

After bloodletting of any considerable magnitude, lactic acid and, it is reported, a small amount of sugar, appears in the urine. Thus Araki[2] found lactic acid in the urine of rabbits which had been bled. He also found lactic acid in the urine of rabbits which had been exposed to the action of rarefied air, and he found lactic acid and dextrose in the urine of animals, the oxygen-carrying capacity of whose blood had been diminished through the respiration of carbon monoxid. It should be noticed in passing that wherever lactic acid is formed in the organism there is a concomitant rise in proteid metabolism. The anemic condition may possibly influence the enzyme which normally breaks up lactic acid, so that its metabolism is not effected. Since this lactic acid is a derivative of dextrose, its non-combustion may raise the proteid metabolism to a higher level, just as is the case when sugar remains unburned in diabetes. This is true in spite of the fact that the total metabolism,

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[1] Pettenkofer and Voit: "Zeitschrift für Biologie," 1869, Bd. v, p. 319.

[2] Araki: "Zeitschrift für physiologische Chemie," 1894, Bd. xix, p 424.

as represented by the heat of combustion of proteid and fat, remains unaltered.

Another fact which has been observed by Lewenstein[1] is that when rabbits are kept in a bell-jar at a barometric pressure of 300 to 400 mm. (corresponding to 5000 to 7500 meters above sea-level) they die on the second or third day and autopsy reveals extreme fatty infiltration of heart, liver, kidney and diaphragm. These animals took no food. The cause of this fatty change, in the present writer's opinion, was the lessened combustion of sugar or its derivative, lactic acid, which always induces an abnormal deposit of fat in any sugar-hungry cells (p. 246).

Kohler[2] artificially compressed the trachea of rabbits by tying a lead wire around it. The animals recovered from the operation and lived for four weeks in a condition of dyspnea. Appetite, weight, urine, and body temperature remained normal almost until the end. The dyspnea was apparently insufficient to affect the metabolism. Increased respiration and heart activity were effectual efforts at compensation, so that there was no lack of oxygen in the animals. However, the altered pressure in the lungs and the prevailing dyspnea brought about a condition of stasis of which the animal died. The secondary alterations were acute and widespread, and were hyperemia of the lungs, vesicular and intralobular emphysema of the lungs, and hypertrophy of both sides of the heart.

In emphysema of the lungs in man, determinations by Geppert and by Speck[3] have shown that the respiratory exchange of gases was entirely within normal limits.

It is evident from these various citations that the general oxidation of the body is normally maintained in anemia and in pulmonary disease, provided the disturbances are not of extreme intensity.

The constantly increasing use of mountain air as a recuper-

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[1] Lewenstein: "Pflüger's Archiv," 1897, Bd. lxv, p. 278.

[2] Kohler: "Archiv für exper. Path. u. Pharm.," 1877, Bd. vii, p. 1.

[3] Cited by Jaquet: "Ergebnisse der Physiologie," 1903, Bd. ii, I, p. 562.

ative force for the wornout individual leads to the inquiry whether the metabolism at high altitudes is different from that at the sea level. For knowledge of this sort we are principally indebted to Zuntz and his pupils. The study of the subject may be taken up by using three different methods: First, the pneumatic cabinet; second, balloon ascensions; third, mountain ascents.

The relative composition of the atmosphere is the same at all distances from the earth's surface. Durig and Zuntz[1] find that the atmosphere at a height of 2900 meters contains carbon dioxid 0.03 per cent., nitrogen 79.11 per cent., and oxygen 20.86 per cent.; whereas, at an altitude of 4600 meters it contains carbon dioxid 0.03 per cent., nitrogen 79.10 per cent., oxygen 20.87 per cent. These are values identical with each other and with those determined at sea-level.

The pressure of the atmosphere varies with the height from the sea-level as appears in the following table:

	Altitude.		
Meters.	Feet.	Miles.	Barometer in Mm. Hg.
0	0	0.	760
1000	3,281	0.6	670
2000	6,562	1.2	592
3000	9,843	1.9	522
4000	13,124	2.5	460
5000	16,405	3.1	406
6000	19,686	3.7	358
7000	22,967	4.4	316
8000	26,248	5.0	297

Fraenkel and Geppert[2] placed a dog, which had fasted seven days, under the influence of greatly diminished atmospheric pressure and found an increased proteid metabolism which continued on the second and third days. They also suspected the presence of incomplete products of combustion in the urine. These results accord with Araki's investigations.

Von Terray[3] finds no change in the respiratory activity of

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[1] Durig and Zuntz: "Archiv für Physiologie," 1904, Suppl., p. 421.

[2] Fraenkel and Geppert: "Ueber die Wirkungen der verdünnten Luft," 1883.

[3] Von Terray: "Pflüger's Archiv," 1896, Bd. lxv, p. 440.

dogs in air containing between 87 and 10.5 per cent. of oxygen. When 10.5 per cent. of oxygen is present an increased respiratory activity commences. With 5.25 per cent. of oxygen there is every indication of lack of oxygen for the tissues, and the elimination of lactic acid in the urine is pronounced. The quantity of lactic acid eliminated was greatest after the respiration of an atmosphere containing 3 per cent. of oxygen. The quantities obtained were 1.206, 1.860, 2.176, 2.300, 2.352, 2.663, 3.020, and 3.686 grams of lactic acid in twenty-four hours. In these cases we again see the analogy of the metabolism to that already cited as having been discovered by Araki after bloodletting in rabbits.

L. Zuntz[1] found that when he respired in a pneumatic cabinet, at an atmospheric pressure of 448 mm. of mercury, that there was no change in his respiratory metabolism as compared with the normal. The results may be tabulated as follows:

Per Cent. O_2 in Air.	Pressure in Mm. Hg.	Respired Per Minute.	
		O_2 c.c.	CO_2 in c.c.
21	758 mm.	231.25	200.15
12	448 mm.	238.7	213.1

This latter experiment was done at a pressure corresponding to a mountain height of 4500 meters. He also showed that variations in atmospheric pressure within the above limits had no effect on the metabolism during muscular exercise.

Von Schrötter and Zuntz[2] made two balloon ascents to heights of 4560 and 5160 meters. Zuntz showed an increased oxygen absorption of 7 per cent. above that at sea-level. In the case of Von Schrötter the increase was slight, except during one interval of shivering when a 20 per cent. increase was recorded. The authors attributed the slight rise in the metabolism to the increased work done by the respiratory muscles. During the higher ascent sugar appeared in the urine of Zuntz, indicating incomplete oxidation.

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[1] Loewi and Zuntz: "Pflüger's Archiv," 1897, Bd. lxvi, p. 477.

[2] Von Schrötter and Zuntz: *Ibid.*, 1902, Bd. xcii, p. 479.

A research of Zuntz[1] on the subject of mountaineering describes how he and Durig ascended to the Col d'Olen (2900 meters), and, having remained there for a week, passed upward to a hut (4560 meters) constructed near the summit of Monte Rosa, the highest mountain of the Alps after Mont Blanc. They lived in this hut two weeks and a half. The height of the barometer was 443 millimeters, which indicates a quantity of oxygen amounting to 12.2 per cent. of an atmosphere. On the Col d'Olen there was no increase in their metabolism when they were resting, and there was no increase in the requirement of energy necessary to accomplish one kilogrammeter of work. This agrees with the results of Bürgi elsewhere mentioned (p. 175). At the higher level, near the summit of the mountain, the resting metabolism increased at once and permanently to the extent of 15 per cent. Zuntz during a former sojourn had noted an increase of 44 per cent. in his metabolism when on the mountain. Exposure to the sunlight was almost without effect on the metabolism. The increased metabolism was not due to cold, for it was present when the individual was in a warm bed in the hut. At sea-level the energy equivalent of three kilogrammeters is liberated in the body in order to lift one kilogram of body substance one meter high. Here on the snow-fields of Monte Rosa Durig required the equivalent of 4.0 to 4.8, Zuntz 5.3 to 6.8 kilogrammeters of energy to accomplish one kilogrammeter of work. This agrees with a former experiment of Zuntz when he was living in the same locality, in which he found that the increased metabolism necessary to effect one kilogrammeter of work in climbing to be 70 per cent. above the requirement for the same work at sea-level.

That L. Zuntz (see p. 217) found no increase in his metabolism, either during rest or work, when he was in a pneumatic cabinet under an atmospheric pressure of 448 mm., is explained by Durig and Zuntz as due to the short length of the experiment.

Not only is the metabolism necessary to accomplish work greater on high mountains than at sea-level, but the capacity

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[1] Durig and Zuntz: "Archiv für Physiologie," 1904, Suppl., p. 417.

for work is greatly reduced. Schumburg[1] found that he could accomplish a maximum of 999 kilogrammeters of work in one minute in Berlin, 619 when on the Monte Rosa glacier, and only 354 kilogrammeters when he was on the top of the mountain. The limit of work on Monte Rosa was therefore one-third what could be accomplished in Berlin.

Durig and Zuntz, Mosso, and others, have found their respiration to be distinctly of the Cheyne-Stokes character after a return to the hut subsequent to exercise in the higher Alps. They found that when they were on Monte Rosa a temporary oppression resulted if their respiration was partly hindered,—as in the case of lacing their boots. Also, strict attention to a definite task might reduce the respiratory activity to such an extent that anemia of the brain, accompanied by dizziness, readily ensued.

Workman[2] reports that normal sleep was impossible when camping in the Himalayas at a height of 19,358 feet (nearly 6000 meters). When the individuals of the party dozed they were awakened gasping for breath. Air at this height contains 10 per cent. of oxygen.

The ventilation of the lungs of Durig and Zuntz while at rest at different altitudes varied as follows:

RESPIRED IN LITERS PER MINUTE.

	ACTUAL.	ZUNTZ. REDUCED TO 760 MM. HG. AND 0° C.	DURIG. REDUCED TO 760 MM. HG. AND 0° C.
Sea-level.....	4.61–5.03	4.15–4.53	5.00–5.63
Col d'Olen...	5.97–6.36	3.99–4.16	3.81–5.07
Monte Rosa..	6.86–8.52	3.71–4.88	4.05–4.60

The actual amount of inspired air appears to be about the same at different altitudes, an increased volume compensating for increasing rarefication of the atmosphere.

The atmosphere in which one lives is really the air within the alveoli (Pflüger). Durig and Zuntz have calculated the pressure of oxygen and carbon dioxid within their alveoli at different

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[1] Zuntz and Schumburg: "Pflüger's Archiv," 1896, Bd. lxiii, p. 488.

[2] Workman: "Bulletin of the American Geographical Society," 1905, vol. xxxvii, p. 671.

levels, and, measured in terms of millimeters of mercury, have found them to be as follows:

	Pressures in Mm. Hg.			
	Zuntz (of Berlin).		Durig (of Vienna).	
	O_2	CO_2	O_2	CO_2
At home—rest	107	36	109	32
At home—ascending walk	109	33	99	37
On Monte Rosa—rest	57	21	53	24
On Monte Rosa—horizontal walk	60	17	55	21
On Monte Rosa—ascending walk	63	18	55	24

It is evident from a study of the results that muscular exercise in all these localities produces an increase in the alveolar tension of oxgyen and a decrease in that of carbon dioxid. This is brought about by the stimulation of respiration.

It will be interesting to examine the evidence of the effect of decreasing oxygen tension on the capacity of the blood in the lungs to absorb oxygen. The usually accepted doctrine that atmospheric air, shaken with blood, will practically saturate the hemoglobin present, rests upon Hüfner's experiments with carefully prepared solutions of hemoglobin. Loewi and Zuntz,[1] however, show that if normal blood be used the saturation is 89 per cent. at the most. On the basis of this newer work, Durig and Zuntz[2] have calculated the saturation of the hemoglobin within the blood at the different altitudes. At Berlin, oxygen exerting alveolar pressures of 113 and 103 mm. would saturate the blood in the lungs to the extent of 81.9 and 80.5 per cent., respectively. On Monte Rosa alveolar oxygen at pressures of 57.0 mm. (Zuntz) and 53.2 mm. (Durig) would respectively cause a saturation to the extent of 69.5 and 68 per cent. The lowest recorded oxygen pressure in the alveoli was 48.3 mm. (Durig), which corresponded to 65.9 per cent. of oxyhemoglobin, and was accompanied by severe headache. A quickened heart-beat produced a more rapid circulation than normal. The experimenters find no ground for believing that there was at any time any real oxygen deficiency in any of the important tissues of the body. They consider that their gradual ascent

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[1] Loewi and Zuntz: "Archiv für Physiologie," 1904, p. 207.

[2] Durig and Zuntz: *Loc. cit.*, p. 442.

from sea-level prevented the usual disturbances of appetite and digestion which are probably caused by anemia in the abdominal region (mountain sickness).

After exercise, however, Zuntz and Durig noted qualitative changes in the metabolism indicating incomplete combustion. This was shown in the reduction of the respiratory quotient below that of fat. The authors say:[1] "The experiments leave no doubt that the increased deficiency of oxygen supply, induced by the greater metabolism of the tissue during exercise, is associated with the cause of the increased requirement of energy."

There is no reference to the presence of either sugar or lactic acid in the urine after exercise on Monte Rosa, substances whose presence one might suspect. Loewi[2] reports an increased excretion of amino acids during mountain sickness or during exercise at these high altitudes.

It is apparent that life at an altitude of 4600 meters is on the borderland between the normal and the dyspneic. Less work can be accomplished, and this at the expense of a greater metabolism, because of the inhibition of the muscle mechanism through the accumulation of imperfectly burned products of metabolism.

Higher mountain ascents have been accomplished than the one here described. The celebrated mountaineer, Whymper, has ascended Chimborazo (6247 meters) without suffering from mountain sickness. Tolerance for highest altitudes depends on individual idiosyncrasy, which has been variously attributed to differences in the capacity of hemoglobin to absorb oxygen, to differences of diffusion power in the alveolar membrane, and to susceptibility to cosmic influences, such as electric and magnetic phenomena.

The discovery of Viault[3] that at an altitude of 4000 meters the number of red blood-cells increased to 7,000,000 and 8,000,000 per cubic mm. of blood appeared at first to indicate

[1] Autorenreferat: "Biochemisches Centralblatt," 1904, Bd. iii, p. 285.

[2] Loewi: "Archiv für Physiologie," 1906, p. 386.

[3] Viault: "Comptes rendus de l'academie des Sciences," 1890, T. cxi, p. 917.

a compensatory increase in oxygen-combining power during life in rarefied air. However, Abderhalden[1] has shown that this phenomenon is due to an expression of blood fluid from the circulatory system and a consequent thickening of the blood, for he finds no change in the total quantity of hemoglobin in animals of the same species when they are killed at different heights. Only after prolonged residence at a high altitude may any increase in the quantity of hemoglobin be possible.[2] Such an increase has been positively shown by Zuntz and his co-workers.[3]

The results of these varied experiments confirm the independence of the metabolism of variations in atmospheric pressure as regards all the customary habitats of mankind. The beneficial properties of mountain air may be largely the same as those derived at watering-places, *i. e.*, outdoor life, cool air, exercise, diversion through change of scene, mental rest, and, finally, mental suggestion of benefits received. The dry, crisp air undoubtedly benefits catarrhal disturbances, which are, on the other hand, aggravated by the climate of the seashore.

In the search for conditions which might reduce the intensity of metabolism, the influence of the internal secretions of the sexual glands has been prominently considered. Careful experiments of Lüthje,[4] however, show that castration in dogs of both sexes has no influence on the metabolism. It is said, however, that removal of the ovaries reduces for a time the number of red blood-corpuscles and it is suggested that ovarian insufficiency may be the cause of chlorosis.[5]

The thyroid gland is a gland whose internal secretion profoundly affects the amount of general metabolism. This influence is apparently brought about by a substance called

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[1] Abderhalden: "Zeitschrift für Biologie," 1902, Bd. xliii, p. 443.

[2] Abderhalden: "Pflüger's Archiv," 1905, Bd. cx, p. 98.

[3] Zuntz, Loewi, Müller, and Caspari: "Höhenklima und Bergwanderungen in ihrer Wirkung auf den Menschen," Berlin, 1906.

[4] Lüthje: "Archiv für ex. Path. und Pharm., 1902, Bd. xlviii, p. 184.

[5] Breuer and v. Seiller: "Arch. f. ex. Path. und Pharm.," 1903, Bd. l, p. 169.

thyroidin which, when produced in normal quantities, maintains the proper functions of the nervous system. A subnormal production reduces the activity of the nervous system and incidentally the quantity of metabolism. An over-production increases the irritability of the nervous apparatus and raises the metabolism. Myxedema is a condition in which the thyroid gland has atrophied and its secretion is no longer available. Exophthalmic goiter presents the opposite phase, since here a superabundance of thyroidin is believed to be produced. Symptoms somewhat akin to the latter condition may be induced by ingesting thyroid extracts in normal animals and man.

Magnus-Levy[1] found the carbon dioxid output increased after giving a normal man thyroid extracts. Fritz Voit[2] finds the same to be true of a dog, and also that more proteid is metabolized. It is this latter action which contraindicates thyroid feeding in obesity. However, Rheinboldt[3] states that a man fed with thyroid extracts may be maintained in nitrogen equilibrium if much proteid be allowed in the diet.

Anderson and Bergman[4] have given large quantities of thyroid extract to a man who was kept in perfect quiet, and no increased output of carbonic acid was noticed. They attribute the increased metabolism which is usually observed to the increased muscle tonus caused by the highly irritated central nervous system. A high metabolism is observed in cases of exophthalmic goiter. Friedrich Müller,[5] reports a case of an individual weighing only 29 kilograms who constantly lost weight notwithstanding a daily diet containing 68 grams of proteid with 58 calories per kilogram. Under such circumstances there is undoubtedly an abnormally high destruction of both proteid and fat. The increased proteid destruction has been attributed to toxic influence of the thyroid secretion.

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[1] Magnus-Levy: "Berliner klinische Wochenschrift," 1895, Bd. xxx, p. 650.

[2] Voit, F.: "Zeitschrift für Biologie," 1897, Bd. xxxv, p. 116.

[3] Rheinboldt: "Zeitschrift für klin. Med.," 1906, Bd. lviii, p. 425.

[4] Anderson and Bergman: "Skan. Archiv für Physiologie," 1898, Bd. viii, p. 326.

[5] Müller: "Deutsches Archiv für klin. Medizin.," Bd. li, p. 361.

It may however be caused by an overheating of the muscle cells due to great heat production.

In myxedema the metabolism is reduced and there is a fall in body temperature. Anderson[1] reports a case of a woman whose metabolism was as low as 1260 calories or 18.8 per kilogram: after treatment for nine months with thyroid extracts the heat production rose to 2099 calories, or 32.3 per kilogram. These latter are normal values. The temperature rose with the increase in metabolism.

Clonic convulsions are a symptom following thyroidectomy, and during these periods the temperature rises. The convulsions are central in their origin, for in the monkey they disappear on sectioning the nerves.

It is possible to explain the reduced temperature as due to disturbances in the nerve mechanism of temperature regulation. The diminished temperature of the body would then be an influence in reducing the metabolism of the cells. This disease is a rare example of a condition in which the metabolic processes are permanently depressed.

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[1] Anderson: "Die physiol. Abtheil. eines klin. Aufsatzes in Hygiea," Stockholm, 1898 (quoted in Tigerstedt's "Lehrbuch der Physiologie").

CHAPTER XII.

METABOLISM IN DIABETES AND IN PHOSPHORUS-POISONING.

It is said that the sweet taste of diabetic urine was familiar to Susruta, a physician who lived in India during the seventh century. The disease, then as now, may have been more prevalent among the Hindoos than elsewhere in the world. In Europe the sweet taste of diabetic urine was discovered by Thomas Willis in 1674, but it was not until another hundred years that Dobson, in 1775, showed that the taste was due to the presence of sugar. Subsequently a hyperglycemia was established.

Claude Bernard found that the stimulation by puncture of a group of cells (the "diabetic center") lying in the medulla near the floor of the fourth ventricle, gave rise to an excretion of sugar in the urine. This experiment is the source of the false impression that diabetes is essentially of nervous origin. It is called *la piqûre.*

Diabetes is a disease of particular interest since it is a departure from the physiological condition involving the capacity of the organism to care for sugar in the normal fashion. All the symptoms are due to this one fact. No disease has been more thoroughly investigated. In presenting the details to the reader, it may be remarked that the work done is prophetic of possible accomplishment along scientific lines in the study of disease. It is typical of that "scientific medicine" which affrights the devoted spirits of a passing empiricism.

The foundation of modern knowledge on this subject was aid by von Mering and Minkowski[1] and by Minkowski[2] alone,

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[1] Von Mering and Minkowski: "Archiv für ex. Path. und Pharm.," 1889, Bd. xxvi, p. 371.

[2] Minkowski: *Ibid.*, 1893, Bd. xxxi, p. 85.

who extirpated the pancreas in dogs and demonstrated that such animals became diabetic.

The causes of the appearance of sugar in the urine are: (1) Either the organism cannot burn sugar, which therefore accumulates in the blood in excess of the normal, and is filtered through the kidney (diabetes mellitus, experimental pancreas diabetes); or (2) some tissues may lose their sugar-retaining function so that the normal regulatory control of the quantity of blood sugar is lost or diminished. (Bernard's piqûre, alimentary glycosuria, phlorhizin glycosuria).

The stimulation of Bernard's "diabetic center" is only effective in its results when the liver contains glycogen.[1] This form of glycosuria cannot be obtained in a starving animal. It is attributed to a sudden flushing of the liver with blood and a conversion of glycogen into sugar, so that hyperglycemia and sugar elimination through the kidney follow.

It is reported that the sight of a cat by a dog confined in a cage may result in the appearance of dextrose in the dog's urine. Assuredly it may here be surmised that great muscular activity on the part of the dog has thrown sugar into the blood in excessive amounts. A glycogen-free dog would scarcely be so affected.

Alimentary glycosuria is seen in normal animals and in man, when sugar is given in larger quantities than the glycogen regulatory function can care for. Moritz[2] finds two grams of dextrose in the urine of a man after the ingestion of 200 grams. Such an alimentary glycosuria lasts between three and six hours.

Hofmeister[3] has discovered that the fasting organism is more susceptible to alimentary glycosuria than the well-fed one. He calls such a condition "starvation diabetes." Evidently an organism whose glycogenic function has not been used is less capable of protecting itself from an excess of dextrose than it is during normal nutrition.

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[1] Dock: "Pflüger's Archiv," 1872, Bd. v, p. 571.

[2] Moritz: "Verhandlungen des 10 Congresses für innere Medizin," 1891, p. 492.

[3] Hofmeister: "Archiv für ex. Path. und Pharm.," 1890, Bd. xxvi, p. 355.

Moritz[1] observed 0.2 to 0.3 per cent. of sugar in the urine of four out of six healthy people who had partaken of a quantity of sweets and champagne.

Evidently such conditions as these are not to be classed with diabetes mellitus, where there is a fundamental disturbance in the sugar-burning power in the organism. It would be of service to distinguish between *glycosurias* where the *sugar-holding* capacity of the organs has been diminished or overstrained, and *diabetes* in which the *sugar-burning* capacity has been affected.

A special type of glycosuria is caused by phlorhizin injections, as was discovered by von Mering.[2] Here the blood itself while passing through the kidney loses the power of retaining its normal sugar content and a hypoglycemia results. Sometimes when the kidney is altered in Bright's disease, phlorhizin is ineffective and no glycosuria follows its administration. The renal character of phlorhizin glycosuria was demonstrated by Zuntz[3] who placed cannulæ in the upper portions of the two kidneys and injected phlorhizin into the renal artery of one. On the injected side, sugar-containing urine appeared in two minutes, and three minutes later the kidney on the opposite side yielded sugar through its ureter. The delay was due to the lapse of time necessary for the transportation of the phlorhizin by the blood stream from the injected kidney to the other one. In this form of glycosuria sugar ingested *per os*, or subcutaneously, or as formed in proteid metabolism, is all eliminated in the urine, provided the quantity given does not flood the organism with sugar.[4] In this latter case part of it can be burned.

Loewi[5] has conceived the idea that the blood sugar is normally in a loose combination with colloid. This colloid sugar cannot pass through the glomerulus. If, however, sugar accumulates in the blood above the combining power of the

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[1] Moritz: "Archiv für klinische Medizin," 1890, Bd. xlvi, p. 217.

[2] Von Mering: "Verhandlungen des 5 Congresses für innere Medizin," 1886, p. 185.

[3] Zuntz: "Archiv für Physiologie," 1895, p. 570.

[4] Stiles and Lusk: "American Journal of Physiology," 1903, vol. x, p. 67.

[5] Loewi: "Archiv für ex. Path. und Pharm.," 1902, Bd. xlviii, p. 410.

colloid, then the crystalloid dextrose readily passes through the kidney. This condition exists in diabetes mellitus. In phlorhizin glycosuria the kidneys break up the colloid sugar, and the sugar may then be eliminated. Stiles and Lusk, while accepting Loewi's theory, have added the hypothesis that the colloid sugar cannot be burned. Phlorhizin acting in the kidney will split the compound and permit the elimination of sugar. Any free dextrose in the general circulation unites with the colloid radical and is protected from combustion, as is the case when five grams of dextrose are administered subcutaneously only to reappear in the urine (Stiles and Lusk). If the quantity of sugar in the blood rises above this combining power, immunity from destruction is lost and the sugar burns. Phlorhizin glycosuria is only temporary in character, and subcutaneous injections of alkaline solutions of the drug three or four times daily are necessary in order to obtain constant results.

The character of phlorhizin glycosuria has been dwelt upon because the total metabolism is here identical with that observed in diabetes mellitus. It has long been known that diabetics eliminate sugar even after all administration of sugar is stopped. It has also been generally recognized that proteid ingestion tends to increase the sugar output in the urine, while fat has no effect.

A large amount of information has been collected concerning the relation between the urinary nitrogen and sugar elimination in the fasting and meat-fed diabetic organism. The dextrose to nitrogen ratio (D : N) is a key to the problem of the quantity of sugar which can be derived from proteid metabolism (p. 112).

Minkowski[1] was the pioneer who discovered that depancreatized dogs, whether fasting or fed with meat, showed a constant elimination of 2.8 grams of dextrose for each gram of nitrogen in the urine. This ratio (D : N :: 2.8 : 1) was the average obtained from seven dogs on twenty-two different days. The lowest ratio was 2.62 : 1, the highest 3.05 : 1. Some other operators have been unable to obtain these ratios. Pflüger[2]

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[1] Minkowski: "Archiv für ex. Path. und Pharm.," 1893, Bd. xxxi, pp. 85, 97.

[2] Pflüger: "Das Glycogen," 1905, p. 491.

finds a variable and generally lower ratio, and his dogs all died of abscesses. Embden's[1] ratios are all lower than Minkowski's, and are probably due to incomplete extirpation of the pancreas.

The accuracy of Minkowski's results is indicated by the fact that the ratio (D : N : : 2.8 : 1) may be easily established by the administration of phlorhizin to rabbits, goats, cats, and in certain dogs whose kidneys have been somewhat affected, as, for example, by giving camphor. Phlorhizin acts first to cause a sweeping out of the excess of sugar in the organism, with a subsequent establishment of the ratio. (See table, p. 235.) The ratios in different animals are given in the following table:

RATIOS IN DIABETES OF D : N : : 2.8 : 1.

	Dog.[2]	Dog.[3]	Cat.[4]	Goat.[5]	Rabbit.[6]
Day.	Pancreas Diabetes.	Phlorhizin and Camphor.	Phlorhizin.	Phlorhizin.	Phlorhizin.
Second day of Diabetes........	..	..	..	2.95	2.89
Third “ “	2.88	..	2.93	2.90	2.69
Fourth “ “	2.94	..	2.80	2.78	..
Fifth “ “	3.09	..	2.93	..	..
Day unknown.................	..	2.8	..	..	..

The uniformity of the ratio as shown in different animals is very striking. One may calculate from these results that 45 per cent. of the proteid molecule may be converted into dextrose in the course of metabolism.

This, however, does not complete the story of the D : N ratio, for a higher ratio or 3.75 : 1 was discovered by Reilly,

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[1] Embden and Salomon: "Hofmeister's Beiträge," 1904, Bd. vi, p. 63.

[2] Minkowski: *Loc. cit.*, p. 97.

[3] Jackson: "American Journal of Physiology," 1902, vol. viii, p. xxxii.

[4] Arteaga: *Ibid.*, 1901, vol. vi. p. 175.

[5] Lusk: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 43.

[6] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1895, vol. i, p. 396.

Nolan, and Lusk[1] in the urine of dogs with normal kidneys after subcutaneous injections of phlorhizin. This ratio was subsequently revised by Stiles and Lusk[2] and found to be 3.65 : 1. The importance of this discovery was enhanced by the finding of Mandel and Lusk[3] that the same ratio may exist in human diabetes when the patient is given a diet of meat and fat. These ratios are thus comparable:

PHLORHIZINIZED DOG.[4]	DIABETES MELLITUS IN MAN.[5]
3.60	3.60
3.65	3.65
3.66	3.66
3.62	

In another place (p. 112) it has been shown that the D : N ratio does not vary after the ingestion of sufficient meat to double the quantity of nitrogen in the urine; the sugar also doubles. The sugar production is therefore proportional to the proteid metabolism, and, apparently, must be derived from proteid.

Various objections have been raised to this statement. Other experiments, however, confirm the above proposition.

Lüthje[6] gave nutrose to a depancreatized dog. Nutrose contains casein but no sugar. The dog weighed 5.8 kilograms and eliminated 1176 grams of glucose during twenty-five days. The tissues of the dog could not possibly have contained over 232 grams of glycogen at the beginning of the experiment. The source of the sugar could not have been the animal's store of glycogen, but must have arisen from either proteid or fat.

Pflüger[7] would have it that fat metabolism is the principal source of sugar in diabetes.

It has already been shown that proteid breaks up into amino acids in the intestines, and that such amino acids when ingested

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[1] Reilly, Nolan, and Lusk: *Loc. cit.*

[2] Stiles and Lusk: "American Journal of Physiology," 1903, vol. x, p. 67.

[3] Mandel and Lusk: "Deutsches Archiv für klin. Medizin," 1904, Bd. lxxxi, p. 479.

[4] *Loc. cit.*, p. 77. (Details, this book, p. 64.)

[5] *Loc. cit.*, p. 479.

[6] Lüthje: "Pflüger's Archiv," 1904, Bd. cvi, p. 160.

[7] Pflüger: *Ibid.*, 1905, Bd. cviii, p. 115.

are the equivalent in metabolism of proteid itself (p. 103). Are such amino acids convertible into dextrose?

Knopf[1] has shown that asparagin given to a diabetic dog yields at least 1.3 grams of dextrose for each gram of its nitrogen metabolized. Stiles and Lusk[2] find that a pancreatic digest of meat, consisting of amino acids, when given to a phlorhizinized dog, yields 2.4 grams of dextrose for each gram of nitrogen. Embden and Salomon[3] find that glycocoll, alanin and asparagin increase the dextrose output in a diabetic dog.

Halsey[4] believes that the leucin complex but not leucin itself will increase the sugar in the urine of a diabetic dog.

Pflüger[5] explains that the amino acids stimulate the fat metabolism in the liver in such a manner as to insure a production of dextrose from fat. This can hardly be correct for it would be a most remarkable arrangement if amino bodies carried to the liver of a starving cat under the influence of phlorhizin, and the same quantity carried to the same locality in a dog with pancreas diabetes, should in both cases stimulate exactly the same sugar production from fat.

A simpler and probably truer conception lies in the theory of a denitrogenization of the amino acids by hydrolysis within the organism and the subsequent synthesis of the oxy-acids into sugar by the liver.

A substance like glycocoll might thus be converted into glycollic acid, and this reduced to glycolaldehyde, a body whose subcutaneous injection leads to an output of sugar in rabbit's urine.[6] Alanin in like fashion would become lactic acid, and this in turn dextrose (p. 292).

Von Noorden[7] suggests that leucin may split into acetone

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[1] Knopf: "Archiv für ex. Path. und Pharm.," 1903, Bd. xlix, p. 123.

[2] Stiles and Lusk: "American Journal of Physiology," 1903, vol. ix, p. 380.

[3] Embden and Salomon: "Hofmeister's Beiträge," 1904, Bd. v. p. 507; 1904, Bd. vi, p. 63.

[4] Halsey: "American Journal of Physiology," 1904, vol. x, p. 233.

[5] Pflüger: *Loc. cit.*, p. 187.

[6] Mayer: "Zeitschrift für physiologische Chemie," 1903, Bd. xxxviii, p. 151.

[7] Von Noorden: "Journal of the American Medical Association," October 28, 1905.

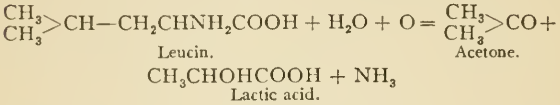
and lactic acid, the latter being converted into dextrose. These reactions might be as follows:

1. $$\underset{\text{Glycocoll.}}{CH_2NH_2COOH} + H_2O = \underset{\text{Glycollic acid.}}{CH_2OH\ COOH} + NH_3$$

$$3\ \underset{\text{Glycolaldehyde.}}{CH_2OHCOH} = \underset{\text{Dextrose.}}{C_6H_{12}O_6}$$

2. $$\underset{\text{Alanin.}}{CH_3CHNH_2COOH} + H_2O = \underset{\text{Lactic acid.}}{CH_3CHOHCOOH} + NH_3$$

$$2\ \underset{\text{Lactic acid.}}{CH_3CHOHCOOH} = \underset{\text{Dextrose.}}{C_6H_{12}O_6}$$

3. 

$$\underset{\text{Leucin.}}{{}^{CH_3}_{CH_3}{>}CH{-}CH_2CHNH_2COOH} + H_2O + O = \underset{\text{Acetone.}}{{}^{CH_3}_{CH_3}{>}CO} + \underset{\text{Lactic acid.}}{CH_3CHOHCOOH} + NH_3$$

In confirmation of the hypothesis that lactic acid is convertible into dextrose, it has been found that the ingestion of lactic acid in diabetes does increase the quantity of sugar in the urine.[1] Mandel and Lusk[2] have shown that *d*-lactic acid, which is the normal lactic acid of the body, may be completely converted into dextrose by the diabetic organism. It has also been found by Embden[3] that if normal blood be perfused through a glycogen-free liver, the sugar content of the blood increases. After varying the procedure he concludes that the normal blood contains substances which are convertible into sugar by the liver. Such substances may be lactic acid, glycolaldehyde, etc. It is therefore probable that the course of the intermediary metabolism involving sugar production is as has been outlined above.

Giving fat with meat to a diabetic will not ordinarily increase the sugar in the urine. The writer has never observed such an increase in any of the work of his laboratory. A large production of sugar from fat has been elsewhere reported[4] and

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[1] Embden and Salomon: "Hofmeister's Beiträge," 1904, Bd. vi, p. 63; A. R. Mandel, "American Journal of Physiology," 1905, vol. xiii, p. xvi.

[2] Mandel and Lusk: "American Journal of Physiology," 1906, vol. xvi, p. 129.

[3] Embden: "Hofmeister's Beiträge," 1904, Bd. vi, p. 44.

[4] Hartogh and Schumm: "Archiv für ex. Path. und Pharm.," 1900, Bd. xlv, p. 11.

Cremer[1] finds that glycerin given alone will increase the output of sugar in the urine.

On giving meat in diabetes the fat metabolism is reduced as it would be in the normal organism, and yet there is no effect on the D : N ratio, and therefore the latter cannot be influenced by the *quantity* of fat burned. This is shown in a respiration experiment made by Mandel and Lusk[2] on a dog with phlorhizin glycosuria whose metabolism starving and after meat ingestion was as follows:

	D : N.	Calories from Proteid.	Calories from Fat.	Calories, Total.
Fasting	3.69	80.2	274.4	354.6
300 grams meat	3.55	161.9	261.7	423.6

The proteid metabolism doubled when meat was ingested, the fat metabolism fell, but the D : N ratio remained constant.

If a production of dextrose from fat metabolism be possible, it must be due to a *qualitative* alteration in the metabolism in rare and special cases. A high authority, von Noorden,[3] writes: "In all *probability* we may even now make the statement that there are a few cases of diabetes in which more sugar is excreted than can be accounted for by the amount of carbohydrate available, and the maximum quantity of proteid that could have been disintegrated, and that in these cases fat must be looked upon as the source of the excess."

A question of special interest is the cause of the two D : N ratios, 2.8 : 1 and 3.65 : 1. The former represents a production of 45 per cent., the latter one of 58 per cent. of sugar from meat proteid. In neither case can dextrose ingested be burned. It is, of course, possible that the sugar production varies under different circumstances; that is to say, the organism (liver ?) may be able at times to produce sugar from a certain class of proteid decomposition products, and at other times not. Or, one may adopt the hypothesis of Mandel and Lusk,[4] which assumes

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[1] Cremer: "Münchener med. Wochenschrift," 1902, Bd. xxii, p. 944.

[2] Mandel and Lusk: "American Journal of Physiology," 1903, vol. x, p. 54.

[3] Von Noorden: "Diabetes," Herter Lectures, 1905, p. 80.

[4] Mandel and Lusk: "Deutsches Archiv für klinische Medizin," 1904, Bd. lxxxi, p. 491.

a difference between α-colloid dextrose and β-colloid dextrose existing in the blood. By α-dextrose is understood the amount of dextrose represented by the ratio D : N : : 2.8 : 1, or 45 per cent. of the proteid. The β-dextrose represents the additional 13.6 per cent. of the proteid, when the ratio 3.65 : 1 is present. The ratio would depend on the combustion or non-combustion of the β-dextrose. If the latter burns, it must do so as a complex, for as free dextrose it would be eliminated in the urine.

This theory of a difference in chemical union would explain the fact discovered by Straub[1] for carbon monoxid "diabetes" and by Seelig[2] for glycosuria following ether inhalation, that sugar appears in the urine in large quantity if a dog be fed with meat, but disappears if the animal be given carbohydrate alone. Seelig found no glycosuria when an intravenous infusion of oxygen was administered at the same time that ether was given. It may be that lack of oxygen causes a dissociation of either α- or β-colloid dextrose derived from proteid, which dextrose then appears in the urine. This suggestion is, however, highly speculative.

One of the very pronounced characteristics of the diabetic is his constant emaciation. There is always a larger excretion of nitrogen in the urine than is necessary for a healthy person. It may be recalled that carbohydrates diminish the proteid metabolism, and also that a person may support life on meat and fat alone without tissue waste. But in this latter case there is a supply of carbohydrate derived from proteid metabolism. This is also true in starvation. But when the proteid sugar is withdrawn from the tissue cells in diabetes, there is at once a largely increased proteid metabolism. This is most obvious in fasting animals treated with phlorhizin, as this glycosuria can be immediately induced. The increase in proteid metabolism is most marked where the higher D : N ratio exists. In this connection the following experiments on fasting animals are suggestive.

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[1] Straub: "Archiv für ex. Path. und Pharm.," 1896, Bd. xxxviii, p. 139.

[2] Seelig: *Ibid.*, 1905, Bd. lii, p. 481.

TABLE ILLUSTRATING THE INFLUENCE OF DIABETES ON PROTEID METABOLISM.

	GOAT.[1]			DOG.[2]		
	D.	N.	D : N	D.	N.	D : N.
Fasting..........	.....	3.72	....	.....	4.04	....
Fasting..........	.....	3.71	....	.....	4.17	....
Fasting and diabetic	20.33	4.90	4.15	63.55	12.66	5.02
“ “	26.08	8.83	2.95	65.30	18.76	3.38
“ “	23.39	8.06	2.90	65.84	18.57	3.54
“ “	19.01	6.84	2.78	64.60	17.29	3.74

In the goat the proteid metabolism rose to 238, in the dog to 450 per cent. of that in the normal animals, as the result of the falling away of the influence of the small quantity of proteid sugar produced in starvation.

In the case of diabetes mellitus reported by Mandel and Lusk, where the ratio D : N was 3.65 : 1 it was found that the ingestion of broths containing 7.7 grams of nitrogen was followed by an elimination of 21.7 grams of nitrogen in the urine or a loss of body nitrogen approximating 14 grams. The patient was greatly emaciated, and passed this day in bed. He could not be maintained in nitrogen equilibrium with 19 grams of proteid nitrogen in the food, but was in nitrogen equilibrium when given 27 grams. In all cases of intense diabetes this factor of an increased proteid metabolism must be considered. In mild cases in which sugar disappears from the urine when carbohydrates are cut out of the food, and in which the patient may burn his proteid sugar, the proteid metabolism is not different from that of a normal person living on meat and fat.

Among the earliest work of Pettenkofer and Voit[3] was a respiration experiment on a diabetic individual. The authors

[1] Lusk: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 43.

[2] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1895, vol. i, p. 397.

[3] Pettenkofer and Voit: "Zeitschrift für Biologie," 1867, Bd. iii, p. 380.

compared the metabolism of a diabetic with that of a normal man, as is indicated in the following table:

COMPARISON OF A NORMAL AND A DIABETIC MAN.

	Grams in the Food.	Grams Burned in the Body.
Healthy man, Proteid	120	120
" " Fat	112	83
" " Sugar	344	344
Diabetic man, Proteid	107	158
" " Fat	108	158
" " Sugar	337	0

(337 grams of sugar in the urine.)

It is seen here that the fat and proteid metabolism are increased in order to compensate for the non-combustion of the sugar. Several years later, on the basis of these experiments, E. Voit calculated that a diabetic on a moderate mixed diet yielded 1015 calories per square meter of surface while the normal individual of similar build produced 1020 calories.

The diabetic condition therefore, does not involve a decrease in the quantity of energy produced, but only an alteration in the source of the energy. This fact can be made still more strikingly apparent by comparing the metabolism of a normal fasting dog with the metabolism of the same dog made diabetic with phlorhizin. Such an experiment was first done by the writer[1] on a fasting dog of 11 kilograms and with the following results:

COMPARISON OF NORMAL AND DIABETIC METABOLISM IN THE SAME FASTING DOG.

	Grams Burned in the Body.	Calories from Metabolism.
Normal, Proteid	20.19	80.68
Fat	55.87	526.13
Total		606.81
Diabetic, Proteid	67.38	128.08
Fat	51.15	481.69
Total		605.77

(39.4 grams dextrose in urine. D : N :: 3.65 : 1)

It is apparent from the above experiment that the proteid metabolism of the diabetic dog increased to 333 per cent. of that

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[1] Lusk: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 31.

of the dog when normal. The fat metabolism slightly decreased, but the total energy derived from the metabolism was exactly the same in both cases.

Rubner[1] has rightly criticised this experiment for neglect to record the temperature at which it was carried out. Rubner has repeated the work when the dog was kept in a room having the temperature of 33°, but the D : N ratio in this dog was only 2.8 : 1 on the second day of diabetes, and Rubner also did not take into account the preliminary clearing out of the body sugar which raised his ratio on the first day. These facts, however, do not invalidate his conclusions.

Rubner finds the metabolism on the fasting days to be the equivalent of 477.8 calories and on the diabetic days to be 510.4, an increase of 32.3 calories per day in diabetes. This increase Rubner attributes to the specific dynamic action of the increased proteid metabolism. This increase in proteid destruction in the diabetic dog amounted to the equivalent of 101.1 calories. Rubner therefore calculates that through the extra metabolism of the equivalent of 100 calories in proteid, 31.9 of extra heat production arises. This agrees with his values elsewhere discussed (p. 137). Rubner's results do not conflict with the writer's experiment, for at a room temperature below 33° the calories of the chemical regulation of temperature are replaceable by those derived from the specific dynamic action of proteid, without any alteration in the total of the metabolism.

The specific dynamic action of proteid ingested in diabetes is also illustrated in the experiment given on page 233. The knowledge at hand makes it possible to estimate the energy value of proteid to the diabetic. It may be calculated from the D : N : : 3.65 : 1 that 52.5 per cent. of the energy in meat proteid is lost to the organism in the form of dextrose. Rubner teaches that 28.5 per cent. of the energy of meat proteid is never utilized in the service of the life processes of the cell, but is liberated as free heat (p. 140). There remains a balance of only 19 per cent. which is actually available for maintenance of the

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[1] Rubner: "Gesetze des Energieverbrauchs," 1902, p. 370.

vital activities in diabetes. The three to fivefold increase in proteid metabolism, however, nearly neutralizes this great waste of energy, and leaves the fat metabolism very much as in the normal organism.

The distribution of the energy from proteid in the diabetic, as described above, may thus be summarized:

100 Proteid Calories.

28.5 for cleavage and denitrogenization.	71.5 for life processes.
Deduct..................	52.5 energy in dextrose.
	19.0 balance available = x.

The production of dextrose from proteid involves the absorption of a good quantity of oxygen. Magnus-Levy,[1] calculating that 60 grams of dextrose arise from those decomposition products of 100 grams of proteid which do not appear in the urine and feces (p. 37), gives the following table indicating the requirement for oxygen when proteid burns in diabetes:

100 grams proteid	= 38.6 C.	4.24 H.	9.24 O.
60 " dextrose	= 24.0 C.	4.0 H.	32.0 O.
Balance requiring respiratory O	+ 14.6 C.	+ 0.24 H.	—22.8 O.

A further calculation showed that the respiratory quotient for proteid in this diabetic condition was reduced from the normal of 0.808 to 0.613. Hence in severe diabetes the respiratory quotient may fall below that representing fat metabolism.

An accompaniment of diabetes which is also present in fasting (p. 63) is the occurrence of acetone, acetoacetic and sometimes β-oxybutyric acid in the organism and in the urine. These substances occur in the absence of dextrose metabolism, and are believed by Geelmuyden[2] to owe their origin to fat metabolism. The quantity of these substances has been held to be a valuable aid in prognosis.[3]

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[1] Magnus-Levy: "Archiv für Physiologie," 1904, p. 379.

[2] Geelmuyden: "Zeitschrift für Physiologische Chemie," 1897, Bd. xxiii, p. 431.

[3] Herter and Wakeman: "New York University Bulletin of the Medical Sciences," 1901, vol. i, p. 8.

However, von Noorden[1] reports cases of diabetics who have excreted 5–6 grams of acetone and 30–40 grams of β-oxybutyric acid in a day, and yet have lived comfortably for years. In the patient of Mandel and Lusk already mentioned, with a D : N ratio of 3.65 : 1 and a complete intolerance for carbohydrates, there was no β-oxybutyric acid and the acetone in the urine was scarcely half a gram (0.8 gram at a maximum). Magnus-Levy[2] has noted as much as 160 grams of β-oxybutyric in the day's urine of a diabetic.

Magnus-Levy was the first to call attention to a close relation believed to exist between the accumulation of β-oxybutyric acid and diabetic coma. Administration of an alkali may delay but does not prevent the onset of diabetic coma. Von Noorden,[3] from experiments of Herter and Wilbur, concludes that the neutral salt of oxybutyric acid is more toxic than has been believed.

Schwarz[4] notes that the administration of butter and of bacon to diabetics increases the acetonuria and that different fatty acids have varying powers of so doing. He finds the lower fatty acids, such as butyric acid, have the greatest effect in this connection, and the higher ones, such as oleic acid, have the least. Such experiments would indicate that oleomargarin with its small content of lower fatty acids is preferable to butter as a food for the diabetic. Schwarz determined the acetone in the breath as well as the acetone and β-oxybutyric acid in the urine.

Curiously enough, Joslin[5] has shown that oleic acid may nearly double the acetonuria in a fasting man, while butyric acid has no effect. Joslin believes that Schwarz's results with higher fatty acids may have been due to the lack of absorption.

The whole question is in an unsettled condition.

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[1] Von Noorden: Von Leyden's "Handbuch der Ernährungstherapie," 1904, Bd. ii, p. 253.

[2] Magnus-Levy: "Archiv für ex. Path. u. Pharm.," 1899, Bd. xlii, p. 232

[3] Von Noorden: "Diabetes," 1905, p. 99.

[4] Schwarz: "Deutsches Archiv für klinische Medizin," 1903, Bd. lxxvi, p. 243.

[5] Joslin: "Journal of Medical Research," 1904, vol. xii, p. 433.

Minkowski[1] noted that the livers of his depancreatized dogs were free from glycogen and this fact has been confirmed by other observers. He also found that when levulose was given, glycogen could be stored. The glycogenic function is inhibited in so far as glycogen production from dextrose is concerned, but it is not destroyed as regards levulose and galactose. This relation may simply indicate that, perhaps through some property of the liver, glycogen is not formed from dextrose when dextrose is needed for the tissues.

Von Noorden[2] states that the inability of the organism to form glycogen is the true cause of the non-combustion of sugar and that sugar to be burned must be polymerized into the higher compound. An argument against this idea is that when the glycogen residual in the fasting organism diabetic with phlorhizin is influenced by tetanus, it is not burned, but it is thrown into the blood and urine as extra sugar (p. 71). This experiment would indicate that the normal utilization of glycogen by the muscle involves its preliminary conversion into sugar.

The present discussion of metabolism in diabetes has been principally directed along lines involving the most intense forms, where the ability to burn sugar is totally absent. It has been observed that there are many intermediary stages in this disease in which the power to burn dextrose is vastly different. To determine the intensity of diabetes, Von Noorden has prepared a standard test-diet which is largely employed in Germany. This diet is divided into portions for three meals. At breakfast and at lunch fifty grams of bread are allowed. The other nutrients are meat, eggs, bacon, butter, green vegetables, cheese, lettuce salad, coffee, and wine. Should the urine of the diabetic be free from sugar on such a diet, the diabetes is mild in character. More bread may then be added to the diet from time to time and the commencement of sugar excretion in the urine watched. When sugar appears the limit of tolerance

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[1] Minkowski: *Loc. cit.*

[2] Von Noorden: "Diabetes," 1905, p. 57.

for carbohydrate has been reached. If, however, the urine contains sugar on the above test-diet, the quantity of bread is reduced, and the urine may then become free from sugar. If the urine contains sugar after all the bread has been removed from the diet, the case is one of severe diabetes. Even here the sugar may disappear from the urine on reducing the proteid in the diet and thereby cutting down one supply of carbohydrate. A diabetic of this order may live on a low proteid dietary with enough fat to furnish sufficient energy for his body's requirement, even as a normal man may exist.

Mandel and Lusk[1] have commended another method for the clinical examination of severe types of diabetes, using the D : N ratio for this purpose. The procedure is as follows: If a diabetic be given a meat-fat diet (rich cream, meat, butter, and eggs) and the twenty-four hour urine of the second day be properly collected,[2] the discovery of 3.65 grams of dextrose to one gram of nitrogen signifies a complete intolerance for carbohydrates and probably a quickly fatal outcome. The authors called this (D : N :: 3.65 : 1) *the fatal ratio.*

A lower ratio of dextrose to nitrogen on this diet indicates that some proteid sugar may be burned. Such a tolerance for sugar may be increased on a meat-fat diet so that the D : N ratio falls, and in favorable cases the dextrose may entirely disappear from the urine.

In the case of the medical student of Mandel and Lusk, the ratio was constantly 3.65 : 1 and the progress of the disease rapidly fatal, death occurring six weeks after the ratio was discovered. In another case of the same investigators, a diabetic was revived from coma with sodium bicarbonate; then, after two days, the meat-fat diet was given. On the second day of this diet the D : N ratio was 2.91:1; on the tenth day, 0.34:1;

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[1] Mandel and Lusk: "Deutsches Archiv für klinische Medizin," 1904, Bd. lxxxi, p. 472.

[2] The urine should be collected so that an early morning hour (before breakfast) terminates the period for one day. This is necessary because the dextrose arising from ingested proteid is eliminated before the nitrogen belonging to the same (p. 111). The long period between the evening meal and breakfast allows for the elimination of both constituents.

on the twenty-third day the patient's urine was free from sugar and he was eating a small amount of carbohydrate. This is an illustration of improving tolerance when a diabetic is placed on a diet which is free from carbohydrates. Good practice calls for the occasional interpolation of periods in which the dietary is free from carbohydrates, on account of the beneficent effect on the power of the diabetic to burn sugar.

The above-mentioned individual now appears to be doing well, two years after the test, but must look carefully to his dietary. His D : N ratio after one week of a strict meat and fat diet is 2.8 : 1, which indicates a less favorable outlook than two years ago. He has not lost in weight.

Physicians will object to this manner of investigation because there is no ready method of determining the nitrogen in the urine. With the growth of laboratories for medical work, this difficulty will be removed. A frequent source of error is the untrustworthiness of the ordinary diabetic patient, who will privately eat carbohydrate in spite of the physician's prohibition.

Having discovered by investigation the tolerance of a diabetic for carbohydrates, the next step is to see that the patient is supplied with a sufficient amount of energy in the food to correspond with the requirement of his organism (35 calories per kilogram). A diabetic with no tolerance for carbohydrates will require between 200 and 250 grams of fat according to his weight. This amount will not be taken unless all the devices of variation in flavor be made use of. The patient will not take it of his own accord, and the amount required should be carefully allotted, preferably in a sanatorium. Diabetics can be educated in such establishments to a proper course of dieting which is the only hope for the amelioration of their troubles. Alcohol may be used, in part, to furnish the necessary calories in the diet.

There is no known cure for diabetes. There is nothing except dieting that affords permanent relief. Opium is said to reduce the sugar output in cases bordering on the severe type.[1]

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[1] Von Noorden: "Diabetes," 1905, p. 158.

The cause of this action is unknown. Experiments inaugurated upon an individual having the 3.65 : 1 ratio might indicate whether its effect was really to increase the combustion of sugar or only to reduce the general metabolism. The ingestion of extracts of different organs does not apparently influence the sugar excretion. Laboratory investigations of the glycolytic power of pancreas extracts have been very numerous, but have failed to give striking results. It is possible that the supposed enzyme is extremely sensitive to a change in normal conditions. Mandel and Lusk gave large quantities of yeast to a diabetic man without changing the D : N :: 3.65 : 1, which shows that the enzymes of yeast are not able to permeate the intestinal wall so that they may replace the natural ferment of the organism.

Minkowski discovered that levulose largely reduced proteid metabolism in the case of depancreatized dogs. This led to the widespread use of levulose in diabetes. Mandel and Lusk, however, found that the increase of sugar in the urine of their diabetic man, after giving 100 grams of levulose, was 80 per cent. of the sugar ingested. The levulose had no effect whatever on proteid metabolism.

Von Noorden[2] confirms this observation. He also states that in severe cases of diabetes, levulose appears in the urine. He believes that levulose is normally produced in metabolism and is normally burned. In very rare cases called levulosuria, levulose alone appears in the urine. One case of complete intolerance for levulose has been reported.[3] Very likely in Minkowski's depancreatized dogs the combustion power for levulose was entirely normal.

The negative results as regards the value of levulose were especially interesting in the case of Mandel and Lusk. This diabetic medical student was confident of the efficacy of levulose on account of opinions expressed by the writer in his lectures. On the days of levulose ingestion the patient's spirits revived,

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[1] Minkowski: *Loc. cit.*, p. 131.

[2] Von Noorden: *Loc. cit.*, p. 50.

[3] Neubauer: "Münchener med. Wochenschrift," 1905, p. 1523.

his strength, measured on the ergograph, decidedly improved and his companions remarked upon the benefit received. All of which shows that subjective sensations are not to be used as scientific criteria.

In this connection it may be mentioned that *d*-glucuronic acid and pentoses have a bearing on carbohydrate metabolism. A large variety of substances (camphor, chloral, turpentine) form syntheses with glucuronic acid in the organism, and corresponding glucuronates are then eliminated in the urine. At first glance glucuronic acid appears to be the preliminary oxidation product of glucose, as is suggested by the following equation:

$$\underset{\text{Dextrose.}}{OHC\,(CHOH)_4CH_2OH} + O_2 = \underset{\text{Glucuronic acid.}}{OHC\,(CHOH)_4COOH} + H_2O$$

However, Mandel and Jackson[1] administered camphor to fasting dogs for several days and noted the excretion of glucuronic acid. On giving large quantities of dextrose the proteid metabolism fell and with it the glucuronic acid elimination; and on giving the animal chopped meat the quantity of camphoglucuronic acid in the urine was correspondingly increased. It may be safely inferred that glucuronic acid is produced solely in the intermediary metabolism of proteid. For the large literature on this subject, and also on the pentoses, the reader is referred to other sources.[2]

Pentoses, which are sugars containing five atoms of carbon, have been detected in animal and vegetable tissue. Hammarsten found a pentose in the nucleoproteid of the pancreas. Neuberg showed that this pentose and the one obtained from nucleoproteid in the liver is *l*-xylose. Grund[3] has found pentoses in all the organs of the body, particularly in those rich in nuclear material.

Salkowski and Neuberg have shown that *l*-xylose may be derived through ferment action on *d*-glucuronic acid. Salkow-

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[1] Mandel and Jackson: "American Journal of Physiology," 1902, vol. viii. Proceedings of the American Physiological Society, p. xiii.

[2] Neuberg: "Ergebnisse der Physiologie" 1904, Bd. iii, 1 Abtheilung, p. 373.

[3] Grund: "Zeitschrift für physiologische Chemie," 1902, Bd. xxxv, p. 111.

ski was the first to detect a pentose in the urine, and this Neuberg has shown to be *i*-arabinose. The elimination of pentoses in the urine may accompany diabetes, but in extremely rare cases a simple pentosuria occurs in which pentose is the only sugar appearing in the urine.

Luzzatto[1] reports such a case in which the elimination of arabinose was independent of diet or mental or muscular effort. Luzzatto believes the pentose in this case to have been *l*-arabinose. Neuberg finds that in the normal rabbit *l*-arabinose is more readily burned than *d*-arabinose. Luzzatto's case could be explained by supposing that the body had lost its normal power to burn *l*-arabinose as normally produced in metabolism.

Pentosuria is occasionally discovered in the routine of life insurance examinations. So far as known it is without danger to general health.

Cremer,[2] in a series of excellent experiments, has shown that a vegetable pentose, such as rhamnose, may be burned in a rabbit and spare an isodynamic equivalent of fat. In one rabbit, on a fasting day, the total metabolism amounted to 129.1 calories (proteid, 22.5 and fat, 106.6), and on the day when rhamnose was given to 128.4 calories (proteid, 21.36; fat, 32.9, and rhamnose 74.11).

Lindemann and May[3] found that 90 grams of rhamnose could be used by a normal man. When, however, rhamnose was given to a diabetic individual whose urine had been sugar free, sugar appeared in the urine. In cases of severe diabetes reported by von Jacksch[4] it was found that rhamnose, arabinose and xylose tended to increase the proteid metabolism, and hence the sugar output, and also brought about diarrhea. The use of pentoses in diabetes has therefore not been successful.

Opie[5] has endeavored to establish a connection between

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[1] Luzzatto: "Hofmeister's Beiträge," 1904, Bd. vi, p. 87.

[2] Cremer: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 428.

[3] Lindemann and May: "Deutsches Archiv für klin. Med.," 1896, Bd. lvi, p. 282.

[4] Von Jacksch: *Ibid.*, 1899, Bd. lxiii, p. 612.

[5] Opie: "Journal of Experimental Medicine," 1901, vol. v, p. 397.

changes in the islands of Langerhans of the pancreas and the cause of diabetes. Janeway and Oertel,[1] von Noorden, and others, have reported autopsies on cases of severe diabetes in which the pancreas appeared perfectly normal. It is not always possible to observe with the microscope the cause of pathological change in function.

On autopsy in diabetes large quantities of fat are found in the liver and muscles. The same is observed in chloroform narcosis when sugar appears in the urine, in anemia, and after respiration of rarefied air, where lactic acid is eliminated in the urine (p. 215), and in phosphorus- and arsenic-poisoning, which are similarly accompanied by an elimination of lactic acid. These phenomena are always associated with an increased proteid metabolism. Fat likewise appears in the mammary glands during lactation (p. 201).

Virchow assumed a fatty degeneration of proteid in which the tissue proteid was converted into fat, as distinguished from a fatty infiltration in which body fat passed into the cells. Much of the earlier writing of Voit is pervaded with the idea of a considerable origin of fat from proteid (p. 120). The idea of a fatty degeneration of proteid in the old sense has been largely overturned by the work of Rosenfeld.[2] Rosenfeld finds that if a dog be starved and then given sheep's fat, and again starved, the ingested fat will be found deposited as sheep's fat in his adipose tissue, while the liver will contain about 10 per cent. of fat, and this characteristic dog fat. If now phosphorus- or phlorhizin-poisoning be induced and the liver be examined, 40 per cent. of fat may be found therein and this in the form of sheep's fat. Hence, in these cases the fat is simply transported to the liver from the fat deposits of the body. The fat in the blood is largely increased.[3] The fat becomes normal in quantity in the liver twenty-four hours after the cessation of the phlorhizin action. It is retransported to the depots of fat deposit.

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[1] Janeway and Oertel: "Virchow's Archiv," 1903, Bd. clxxi, p. 547.

[2] Rosenfeld: "Ergebnisse der Physiologie," 1903, Bd. ii, I, p. 50.

[3] B. Fischer ("Virchow's Archiv," 1903, Bd. clxxii, pp. 30, 218) reports a case of coma diabeticum in which the blood serum contained 23 per cent. of fat.

If a fatty "degeneration" were to be found anywhere, it would certainly be looked for in the dying cells of the phosphorus liver, or in the analogous condition of acute yellow atrophy of the liver. But another explanation avails.

Mandel[1] has shown that lactic acid disappears from the blood and urine of a phosphorized dog if phlorhizin glycosuria be induced. The writer believes that the lactic acid which occurs is derived from the sugar formed in proteid metabolism. In the above case the sugar is removed before its conversion into lactic acid. In phlorhizin diabetes, dextrose does not burn; in phosphorus-poisoning lactic acid derived from dextrose does not burn. In both cases a sugar-hungry cell, or one where carbohydrate is not oxidized, is found, and under these circumstances fat is attracted to the cell, and in larger quantities than can be useful. Wherever sugar freely burns this fatty infiltration is impossible (p. 143). A reduced local circulation in a portion of the heart may produce anemia of the part, an imperfect local combustion of lactic acid normally formed, and a fatty infiltration of the locality. The writer offers this general hypothesis as his explanation of fatty changes in tissue in general.

It has been stated that the action of phosphorus is to induce autolysis (self-digestion) of the body's protoplasm (Jacoby,[2] Waldvogel[3]), since leucin, tyrosin, and other amino acids may be eliminated in considerable quantity in the urine. Oswald[4] thinks that phosphorus destroys or weakens the antiautolytic agents of the body. That autolytic enzymes do not gain free control over the cells through the direct influence of phosphorus, is proved by the work of Ray, McDermott, and Lusk.[5] These authors found that phosphorus injections raised the proteid metabolism of fasting dogs to 250, 260, 283, 248, 183, and

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[1] Mandel: "American Journal of Physiology," 1905, vol. xiii, p. xvi.

[2] Jacoby: "Zeitschrift für physiologische Chemie," 1900, Bd. xxx, p. 174.

[3] Waldvogel: "Archiv für klinische Medizin," 1905, Bd. lxxxii, p. 437.

[4] Oswald: "Biochemisches Centralblatt," 1905, Bd. iii, p. 365.

[5] Ray, McDermott, and Lusk: "American Journal of Physiology," 1899, vol. iii, p. 139.

164 per cent. of that of the dog when normal. They contrasted this increased proteid metabolism with that obtained in phlorhizin glycosuria, which is represented by increases to 540, 450, 340, and 340 per cent. When, however, they gave phlorhizin and obtained the increased metabolism, and then injected phosphorus, this was not followed by any marked increase in proteid metabolism. Under these circumstances phlorhizin glycosuria is the predominating factor, removing the dextrose produced from proteid. As regards phosphorus-poisoning Araki[1] believes that lactic acid accumulation is due to lack of oxygenation of the tissues caused by a slow heart-beat, but not due to anemia. He does not believe the oxygen deprivation to be very pronounced. The writer offers the explanation that phosphorus may affect the enzyme which breaks up the lactic acid derived from dextrose, and the accumulation of this acid may prevent the action of some of the denitrogenizing enzymes; and further, its non-combustion may necessitate an increase of proteid metabolism.

This theory is strengthened by the discovery of Schryver[2] that the addition of lactic acid favors the accumulation of amino acids in autolysis of the liver.

Claude Bernard showed that dextrose, whether derived from proteid or starch, was convertible into glycogen, and this again was changeable back into dextrose. Present knowledge adds lactic acid to both ends of this chain in showing the following possible progression of events,—lactic acid, dextrose, glycogen, dextrose, lactic acid.

Quite pertinent to this theoretical discussion is the observation of von Jacksch[3] on a patient who recovered from phosphorus-poisoning, and in whom a desire for carbohydrates marked the beginning of convalescence.

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[1] Araki: "Zeitschrift für physiologische Chemie," 1892, Bd. xvii, p. 337.

[2] Schryver: "The Bio-Chemical Journal," 1906, vol. i, p. 153.

[3] Von Jacksch: "Zeitschrift für physiologische Chemie," 1903, Bd. xl, p. 123.

CHAPTER XIII.

METABOLISM IN FEVER.

By fever is generally understood a complex of phenomena whose dominant characteristic is a rise of body temperature. If the term fever be confined simply to the latter aspect, one might classify fevers as follows:

(1) *Physiological fever*, induced, for example, by immersion in a hot bath at a temperature of 40°, which prevents the normal loss of body heat through radiation and conduction. (2) *Neurogenic fever*, as brought about by the direct stimulation of nerve-cells in the *corpora striata* of the mid-brain. (3) *Aseptic fever*, due to the resolution of blood-cells or crushed tissue in the organism. (4) *Infective fever*, produced after the infection of the organism by certain bacteria or their products and by some protozoa. Or, one may consider fever as being due to infection by bacteria or protozoa, and include all other increases of temperature under the term of hyperthermia.

In a previous chapter the mechanism of normal heat regulation has been explained. It was there noted that on a warm, moist day the temperature of a fat individual, when he was working hard, rose considerably above the normal. This effect, if carried to an extreme, results in *sunstroke*, where the overheating of the body causes a rapid pulse, accompanied by dizziness, delirium, or unconsciousness. But in the great majority of cases the body temperature remains delicately balanced, notwithstanding changes in outside environment, or internal heat production. In the fat person at hard work the condition of increased metabolism is combined with that of difficult discharge of heat. A person placed in a bath at 40° would be subject to conditions where there could be no heat loss but rather a gain in heat, even though his metabolism were low. In a normal person, therefore, a rise in temperature may be due to increased heat production, with difficulty in discharging it, or a check of heat loss may be the only factor of the higher temperature. In the discussion of fever one is confronted by two possible factors: (1) an increase in heat production, and (2) a decrease in the facilities for the discharge of heat produced.

It has already been set forth that the metabolism in a cold-blooded animal increases with the temperature of his environment. Warmed tissue metabolizes more material than cooled tissue. It is therefore to be expected that the metabolism in an organism which has been warmed to fever heat will be greater than the normal. This was beautifully shown in the experiments of Pflüger,[1] who subjected both curarized and normal rabbits to external warmth which raised their temperatures. In the animals whose voluntary muscles were paralyzed by curare, as the rectal temperature rose from 39° to 41°, the oxygen absorption increased 10 per cent. for each degree of temperature increase. In the normal animals the increased metabolism between temperatures of 38.6° and 40.6° was shown by increases of 5.7 per cent. for oxygen, and 6.8 per cent. for carbon dioxid for a rise of one degree of temperature.

It has been noted in another chapter (p. 93) that Rubner found in man that a bath at a temperature of 35° had no effect on metabolism, while one at 44° increased the volume of respiration 18.8 per cent., the oxygen absorption 17.3 per cent., and the carbon dioxid elimination 32.1 per cent. Linser and Schmid[2] confirm these results in experiments on two men suffering from *ichthyosis hystrix*, which involved almost complete loss of function of the sweat glands. The body temperature of these men could be varied by altering the temperature of their living room between 30° and 38°. The humidity of the room was from 40 to 50 per cent. The maximum increase in the metabolism of these individuals is represented by a rise in carbon dioxid

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[1] Pflüger: "Pflüger's Archiv," 1878, Bd. xviii, pp. 303, 356.

[2] Linser and Schmid: "Archiv für klinische Medizin," 1904, Bd. lxxix, p. 514.

excretion from 3.8 c.c. per minute and kilogram at the body temperature of 36.2° to 5.3 c.c. per minute and kilogram at 39°. The number of respirations, which were from 12 to 15 per minute at 36°, increased to 20 and 22 at 39°. The total increase in the carbon dioxid output, due to a rise of 3° through simple warming of cells, amounted to 40 per cent.

The next question is of the nature of the materials which are oxidized. It has long been known that urea excretion is abnormally high in fever, and this led to the inquiry whether the cause was merely the result of increased body temperature or due to toxic influences. Thus, Schleich[1] finds that a man in nitrogen equilibrium is affected by an hour's bath in water between 40.5° and 41.5° which causes his temperature to reach 39.7°, so that his nitrogen metabolism for the day increases 18, 22, and 37 per cent. Other authors have not found any increase, but Linser and Schmid[2] explain these divergences of opinion by showing that an increase of body temperature to 39° in man has no effect on proteid metabolism, but that above this there is always an increased destruction of proteid. They therefore conclude that in toxic fevers where the temperature is not above 39° any increase of proteid metabolism must be due to the toxic processes and not to the hyperthermia.

F. Voit[3] found that on artificially raising the temperature of a fasting dog to 40° or 41° for a period of twelve hours, there was an increase in nitrogen elimination of 37 per cent. above the normal. Warming for a period of only three hours had slight effect. If, however, the animal were fed with meat and fat, warming increased the proteid metabolism only 4 per cent. If the animal were given 30 to 40 grams of cane sugar, no increased metabolism of proteid followed the rise in temperature to 41°. It is apparent that the ingestion of proteid and carbohydrates may control this rise in proteid destruction due

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[1] Schleich: "Archiv für ex. Path. und Pharm.," 1875, Bd. iv, p. 90.

[2] Linser and Schmid: *Loc. cit.*

[3] Voit, F.: "Sitzungsberichte der Gesellschaft für Morphologie und Physiologie," 1895, Heft ii, p. 120.

to a febrile temperature. F. Voit explains the increase in proteid metabolism in hyperthermia as due to the quick combustion of glycogen and the consequent impoverishment of the tissues as regards carbohydrate material. Proteid or carbohydrate ingested furnish the necessary carbohydrate and prevent the hyperthermal rise in proteid metabolism. The destruction of proteid due to toxic processes cannot be so easily controlled, as will be seen later.

If certain portions of the brain be punctured, and particularly the region of the *corpora striata*, a high fever sets in. Here again there is an increased output of carbon dioxid and a rise in proteid metabolism. This phenomenon has been recently investigated by Hirsch, Müller, and Rolly[1], and by Rolly[2] alone. They find that after the "heat puncture" of the corpora striata the liver, blood and skin become warmer than the muscles, although normally the muscles are warmer than the skin. They find that the heat puncture is effective even in curarized animals, where the muscles are free from nerve stimuli. Rolly finds, however, that the heat puncture is unsuccessful if the liver of the rabbit has been previously freed from glycogen by strychnin convulsions. Under these circumstances there is no rise in temperature nor concomitant rise in proteid metabolism. The inference is that the fever in question is due to nerve impulses which increase the metabolism of carbohydrate in the liver. In infectious fever there is little glycogen in the organism, but that the fever in this case is due to other causes than the rapid combustion of carbohydrates was shown by Rolly, who infected a rabbit, which had been freed from glycogen as above described, with a culture of pneumococci and obtained as great a rise in temperature and proteid metabolism as would have occurred had the tissues of the rabbit been rich in carbohydrates. The rise in temperature after puncture of the corpora striata may be termed *neurogenic fever*, and it is like its companion, the glycosuria following Claude Bernard's puncture, in that its mechan-

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[1] Hirsch, Müller, and Rolly: "Deutsches Archiv für klin.Med.," 1903, Bd. lxxv, p. 264.

[2] Rolly: *Ibid.*, 1903, Bd. lxxviii, p. 250.

ism is no more invoked in true infectious fever than are the nerve centers in diabetes mellitus (p. 226).

If the extent of metabolism in infectious fevers be investigated and compared with that found in simple hyperthermia, a very analogous state of affairs is discovered. The course taken by the metabolism in toxic fevers is, as a rule, (1) a slight rise in proteid metabolism, even before the fever sets in; (2) increased metabolism with heat retention and increased proteid destruction; (3) heat production and heat outgo become equal, with the body at a higher temperature level. These factors are illustrated in the experiments of May[1] on fasting rabbits injected with a culture of erysipelas of the pig. The results of these respiration experiments with three rabbits, in which the normal, transition, and fever periods were investigated, are given below.

METABOLISM IN FEVER IN RABBITS (May).

Rabbit	Day of Fast.	Body Temperature.	Calories.			
			Total.	From Proteid.	From Fat.	Remarks.
E	3	39.2–39.5	61.9	18	44	Normal.
	4	39.7–41.2	63.9	19	45	Injection.
	5	41.2–40.7	73.3	27	46	Fever.
G	3	38.5–38.2	53.8	16.8	37	Normal.
	4	38.2–38.6	54.0	18.5	35.6	"
	5	38.6–38.6	55.4	20.6	34.8	Injection.
	6	38.7–40.1	61.2	27.9	33.3	Fever.
H	3	39.0–39.6	64.5	10.7	53.8	Normal.
	4	39.6–39.2	64.2	10.4	53.7	"
	5	39.7–41.0	65.8	11.8	54.0	Injection.

The above table shows a slight increase in the proteid metabolism on the day of infection. It also shows that a high fever may be reached by the end of the twenty-four hours after the injection without materially altering the heat production of the day. It demonstrates that on the day of continued fever

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[1] May: "Zeitschrift für Biologie," 1894, Bd. xxx, p. 1.

the metabolism increases, and this at the expense of an increased destruction of proteid, while the fat consumption remains unaltered. A calculation shows that on the days of high fever 20 per cent. more energy was produced in rabbit E, and 15 per cent. more in rabbit G, than on normal days. Since Traube's writings on the subject, the cause of fever has been attributed, not to great heat production, but to a disturbance in the mechanism for the regulation of heat loss. On recalling the fact that the metabolism of a fasting dog may be raised from 100 calories in starvation to 189 calories after giving meat (p. 129), without any change of body temperature, it becomes evident that the rise in metabolism in fever is too insignificant to be the cause of the rise in temperature. In fact, as has been already set forth, the rise in body temperature from failure of the physical regulation may of itself explain the increase in heat production. Thus a calculation made in the case of rabbit E shows that the carbon dioxid elimination is increased 6.6 per cent. for each degree of rise in temperature, which corresponds to Pflüger's experiments, before mentioned, in which artificially warmed normal rabbits excreted 6.8 per cent. more carbon dioxid for each degree of rise in temperature.

Long before May's experiments, Wood[1] had found an average increase of 23 per cent. (calculated by Welch) in the heat production of fasting dogs after inducing fever; and he also found that mere ingestion of food by a normal dog would cause a greater heat production than fever itself.

Traube attributed the cause of fever to a cramp-like constriction of the peripheral arterioles which prevented the proper distribution of blood at the surface, and therefore hindered the normal cooling of the body.

The effect of a cold bath upon a vigorous man is to constrict the peripheral blood-vessels and to increase the heat production. The body temperature, instead of falling, may rise for eight or ten minutes and then sink.[2] If the individual pass from the bath

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[1] Wood: "Fever," Philadelphia, 1880.

[2] Lefévre, J.: "Comptes rendus soc. biol.," 1894, T. 46, p. 604.

during the earlier minutes the hot blood comes to the surface to be cooled, and the body glows with a red color, the so-called "reaction." This experiment shows that there are factors invoked during the first few minutes which prevent the discharge of the heat produced. One factor must be a general constriction of the peripheral arteries, causing the blood to remain in the heat producing inner organs of the body. In this experiment, therefore, cooling of the organism is prevented by the mechanism of physical regulation above described, and the mechanism of chemical regulation which reflexly increases heat production.

To combat a rise in temperature, however, the only means available is the physical regulation,—*i. e.*, the distribution of the blood and the production of sweat. If these avenues of heat loss be diminished or shut off, heat accumulates within the body and temperature rises. How an increase in heat production of 89 per cent. may not cause a rise in temperature in a normal animal has already been described; whereas, a high fever may be accompanied by an increased metabolism of only 15 per cent. The cause of the fever must therefore be due to diminution in the ability to discharge the heat produced.

In further support of this, Senator has shown that the fever following pus injections in a dog begins with a retention of heat within his body. Nebelthau[1] found that when the heat discharge of a normal rabbit was called 100, during the first twelve hours of infection in which the temperature rose from 38.6° to 40.1°, the discharge of heat was but 96.3. Assuming the heat production to have been the same in these two periods (as was actually the case in the rabbits of May) then the heat retained would account for the pathological increase in temperature. At a later stage the discharge of heat rose to equalize its production at the higher temperature.

Nebelthau has shown a fall in temperature and heat production in a rabbit whose cord was divided between the sixth and seventh cervical vertebræ, and has also demonstrated that under

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[1] Nebelthau: "Zeitschrift für Biologie," 1895, Bd. xxxi, p. 353.

these circumstances infection with erysipelas of the pig had no influence on temperature or heat production. The inference is that the febrile toxins act through the higher vasomoter centers, whose regulatory control is lost in the above experiment.

A kindred interpretation may be placed on the experiments of Mendelson,[1] who was unable to produce fever through pus injections when the dog was under the influence of chloral or morphin, although such treatment in a normal animal caused a rise in temperature of from 36.3° to 39.9° in forty-five minutes. Mendelson also finds a constant constriction of the renal blood-vessels in fever.

Further experimentation convinced Sawadowsky[2] that fever could not be produced after the mid-brain was severed from the medulla, whereas if the mid-brain be left intact but the cerebrum be sectioned from it, fever may be induced in the ordinary course. The toxic substance must therefore act on nerve-cells in the mid-brain, which in turn stimulate the medullary centers.

At times during high fever the skin may be red and the peripheral blood-vessels distended. Although there is no sufficient explanation for this, Krehl[3] suggests that the quantity of blood flowing through the vessels at the time may be inadequate to reduce the body's temperature.

The second means of physical regulation of the body temperature is through the evaporation of water both from the lungs and the sweat glands. It might be surmised that the activity of this mechanism was reduced in fever. Nebelthau[4] has shown that the heat lost by evaporation of water, and by radiation and conduction, bore exactly the same ratio to each other in normal and in fever-infected rabbits. Since Rubner (p. 90) has proved that the elimination of water in normal animals greatly increases at high temperatures, the mere maintenance of the usual water evaporation during fever would of itself be abnormal.

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[1] Mendelson: "Virchow's Archiv," 1885, Bd. c, p. 274.

[2] Sawadowsky: "Centralblatt für medizinische Wissenschaft," 1888.

[3] Krehl: "Pathologische Physiologie," 1904, p. 453.

[4] Nebelthau: *Loc. cit.*

No complete metabolism experiment on a man suffering from high fever has ever been made, and here is an opportunity for some one to perform a rare service. By no means the least interesting phase of such an experiment would be the course of water elimination from the skin.

Lang[1] has shown that the elimination of sweat is reduced during the rise of temperature in man, but at the height of fever is the same as the normal, while there is some increased evaporation from the lungs.

Recent experiments by Schwenkenbecker and Inagaki[2] show that the "insensible perspiration" in fever is as great as in health, and that although the urine may decrease in quantity there is no actual accumulation of water in the body as was believed by von Leyden.

Lang[3] has also shown that the secretion of sweat is increased 50 per cent. after the ingestion of food as against an increase of 70 per cent. in the normal individual.

In intermittent fever profuse perspiration is certainly an important factor in the reduction of temperature at the end of the febrile stage.

It may be concluded, as Krehl emphatically states, that insufficiency of water evaporation plays a not unimportant rôle in the febrile rise in temperature. The body might be cooled were the sweat glands freely active.

The production of heat in fever may be greatly increased during a chill, and a rapid rise in temperature may follow. This was shown by Liebermeister[4] in a case of malaria. The temperature rose from 36.9° in the first half hour to 39.5° at the end of another hour, while the carbon dioxid expired rose from 13.85 grams to 34.20 grams per half hour. This was a case of chill with shivering. This increased metabolism is due to the

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[1] Lang: "Archiv für klinische Medizin," 1903, Bd. lxxix, p. 343.

[2] Schwenkenbecker and Inagaki: "Archiv für ex. Path. und Pharm.," 1906, Bd. liv, p. 168.

[3] Lang: *Loc. cit.*

[4] Liebermeister: "Deutsches Archiv für klinisches Medizin," 1871, Bd. viii, p. 153.

mechanism of chemical regulation. The blood is driven from the skin by vaso-constriction, those end-organs of the skin which are sensitive to cold are strongly stimulated, with the result that there is a reflex increase of heat production. That this is true is shown by the fact that if the cold stimulation be removed by supplying a warm environment, the attending phenomena pass off (Krehl.)[1]

Any muscular exercise, such as sitting up, increases metabolism, and may under some circumstances cause a rise in temperature in fever. The diurnal variation of temperature is similar in character to that of health, but its fluctuations are much more extreme, on account of the increased excitability of the vasomotor control of the discharge of heat. The parallelism between the amount of the metabolism and the height of the temperature during the day is shown in Fig. 9, taken from Riethus.[2]

It is apparent that cold and muscular work increase metabolism and temperature in fever, and it may be also surmised that large proteid ingestion, which by its specific dynamic action increases heat production, will likewise increase the body's temperature at a time when heat discharge is difficult (p. 140).

May[3] summarizes the conditions of metabolism in fever in the following statement: "There is an increased proteid metabolism but no increased fat metabolism, except such as may incidentally result from dyspnea, chill, or muscular activity."

Infectious fevers are characterized by a toxic destruction of body proteid. Sometimes, as in the earlier stages of tuberculosis, this tissue destruction may be present in the absence of fever itself. Such a toxic action on body proteid is also observed in cancerous cases, as was described by Fr. Müller.[4] Müller writes: "In the seven cases (of carcinoma) cited, the

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[1] Krehl: "Pathologische Physiologie," 1904, p. 452.

[2] Riethus: "Archiv für ex. Path. und Pharm.," 1900, Bd. xliv, p. 239.

[3] May: Ott's "Chemische Pathologie der Tuberculose," 1903, p. 355.

[4] Müller, F.: "Zeitschrift für klinische Medizin," 1889, Bd. xvi, p. 496.

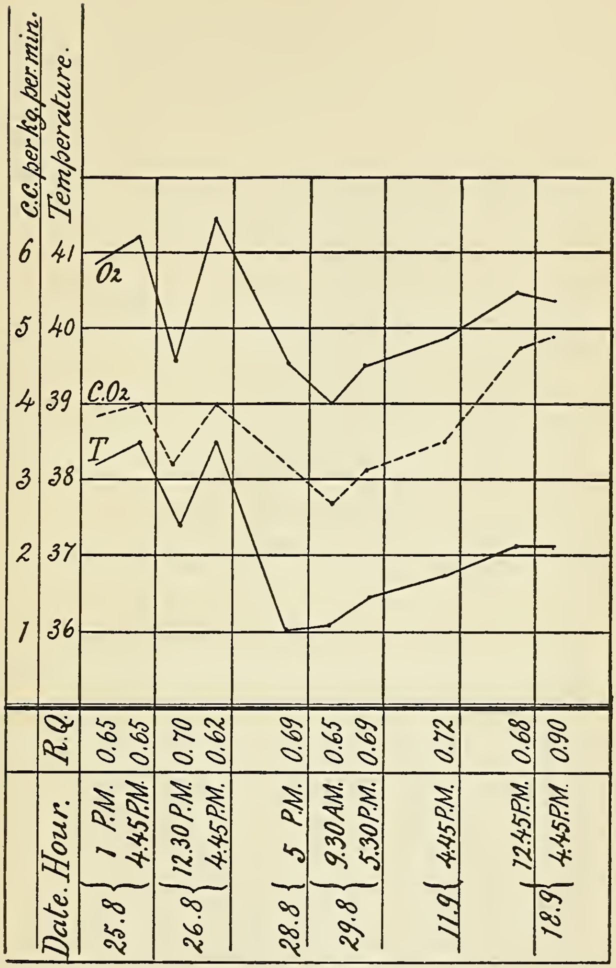

Fig. 9.—Case of abdominal typhoid (Riethus). The figures 1 to 6 on the left represent the amount in c.c. of CO_2 and O_2 of respiration per kilogram and minute. The measurements were all made during fasting. The O_2 curve may be considered as nearly proportional to the heat production (p. 32).

nitrogen excretion was larger than the nitrogen ingestion and consequently the body lost proteid. In two cases the proteid loss was no greater than in healthy individuals with similar insufficient nourishment. In all the other cases the proteid metabolism was decidedly above that of healthy men under the same conditions. Even an ample dietary was not able to establish nitrogen equilibrium. As more food was given the nitrogen elimination rose higher and higher, but the point of nitrogen equilibrium seemed unattainable." Müller compared the cachexia of carcinoma with that found in febrile processes and believed them to be analogous.

As regards tuberculosis May[1] writes: "Larger quantities of the toxins produce, with certain exceptions, a direct injury to the cell protoplasm. They are strongly toxic. The quantity of proteid destruction attributable to this cause is not very large and becomes of importance only when continued for a long period of time and where there is no compensatory regeneration. It appears that the power to regenerate on the part of these cells which are destroyed by toxins is greatly reduced and in severe cases entirely lost."

Other fevers show a high toxic destruction of proteid. F. Müller[2] reports a daily loss of 10.8 grams of nitrogen (equal to 318 grams of muscle) by a typhoid patient during eight days of fever. During fever in croupous pneumonia, the proteid metabolism is much higher than normal. After the crisis there is still a large excretion of nitrogen in the urine which continues until the croupous exudate has been decomposed by autolysis, absorbed by the blood, and metabolized in the body (epicritical nitrogen elimination). In acute pneumonic phthisis (galloping consumption), with its caseous transformation of lung tissue, there is a very high waste of tissue proteid. F. Müller[3] has shown that while the croupous exudate readily undergoes auto-

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[1] May: Ott's "Chemische Pathologie der Tuberculose," 1903, p. 335.

[2] Müller, F.: "Centralblatt für klinische Medizin," 1884, No. xxxvi.

[3] Müller, F.: "Verhandlungen des 20 Congresses für innere Medizin," 1902, p, 192.

lysis at a temperature of 40°, with the production of deutero-albumoses, lysin, leucin, tyrosin, etc., the caseous mass does not undergo autolysis although it permits free diffusion of soluble material, such as phosphates. Hence, although the proteid of the cheesy mass is insoluble in the organism, the soluble toxins may be absorbed from the diseased part, and be the causative agent of the rapid destruction of body proteid in galloping consumption.

The above analysis of metabolism in fever shows that the small increase in total metabolism is associated with increases in proteid metabolism due (1) to the high temperature, and (2) to the virulence with which toxins attack the body tissue. It has been shown that carbohydrate ingestion may reduce the proteid destruction due to the overheating, and that toxic destruction may or may not be compensated for by regenerative processes. Upon this general knowledge it is possible to construct a dietary schedule for the patient.

In all fevers the septic products act upon the hunger centers in the brain, and appetite is wanting. This is evidenced throughout the course of tuberculosis, for example, and tends in this case to weaken the body's resistance through undernutrition. Forced feeding is therefore resorted to.

The experiments of von Hösslin[1] strongly affirmed the beneficence of a liberal diet in ordinary fevers. He writes: "The results show that febrile patients, or at least those who do not run temperatures above 40° to 40.5°, can digest and absorb the total amount of proteid, fat and carbohydrates which can be given them with their diminished appetite, provided the food is administered in a proper form. Temperature and metabolism are only slightly increased thereby."

A milk diet is the usual course prescribed in fevers. Since milk is the proper diet for a rapidly growing calf, its proteid content is extremely high. The relative quantity of this ingredient may be reduced by modifying the milk through the addition of milk sugar or cream. In this way von Leyden and Klem-

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[1] Von Hösslin: "Virchow's Archiv," 1882, Bd. lxxxix, p. 317.

perer[1] have added 5 per cent., then 7.5, and finally 10 per cent. of milk sugar to whole milk. The last named quantity raises the calorific value by 410 calories per liter, and makes a milk containing 1050 calories per liter. Two liters of such milk would be nearly or quite sufficient to cover the requirement of an individual confined to his bed. A milk so prepared may be given to most patients without producing diarrhea or indigestion. The taste is perfectly agreeable to the patient. In this way carbohydrates which are highly desirable in the febrile condition can be properly administered. Von Leyden and Klemperer have also found that an addition of cream to milk, so that its value is increased by 2.5 per cent. of fat, or 225 calories per liter, is favorably received by the patient. Such a milk diet may be fortified by the addition of brandy, whiskey, or sherry. This increases the calorific value of the milk, but more particularly gives it taste, and both through the awakening of the sense of appetite and through direct action upon the neuro-secretory apparatus of the digestive tract, favorably influences the digestion of the food.

It seems strange that in this country where so much attention has been paid to the modification of infant food, the preparation of suitable diet in fever should have received such scant attention. It may well be that investigation will show that dilution of milk and its fortification by ingredients other than proteid may be as advantageously practised in fever cases as in infant nutrition.

The discussion now turns from these theoretical considerations to the actual results of nutritive investigations in fever as presented by von Leyden and Klemperer.

The following table represents a case of a typhoid fever patient to whom milk fortified with meat powder was given, thereby producing a high proteid diet. The quantity of the individual nutrients, the calorific value of the diet, and the nitrogen in the urine and feces were determined. The daily

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[1] Von Leyden and Klemperer: Von Leyden's "Handbuch der Ernährungstherapie," 1904, Bd. ii, p. 345.

loss of body nitrogen was calculated. The results were as follows:

METABOLISM IN ABDOMINAL TYPHOID. DIET HIGH IN PROTEID.

Highest Temp.	Food.					Excreta.			Loss of Body N.
	Amount in Grams.	Calories.	N.	Fat.	Carbohydrates.	Urine N.	Feces N.	Total N.	
39.6	600 milk.	408	3.2	21	27	15.76	0.42	16.18	12.98
39.8	1000 milk.	680	5.36	35	45	18.96	0.42	19.38	14.02
40.2	900 milk, 20 meat-powder.	686	7.67	31	40	17.88	0.42	18.30	10.63
39.7	1200 milk, 50 meat-powder.	1002	13.61	42	54	21.56	1.75	23.31	9.70
39.9	1500 milk, 100 meat-powder.	1392	22.45	52	67	28.7	1.75	30.45	8.00
40.3	1200 milk, 50 meat-powder.	1188	20.86	42	54	27.9	1.75	29.65	8.79
40.3	1500 milk, 50 meat-powder.	1206	15.2	52	67	21.7	1.92	23.62	8.42
39.8	2000 milk, 50 meat-powder.	1546	17.85	70	90	22.9	1.92	24.82	6.97
40.2	2000 milk, 100 meat-powder.	1732	25.1	70	90	29.6	1.92	31.52	6.42
39.9	2000 milk, 50 meat-powder.	1546	17.85	70	90	20.85	2.13	22.98	5.13
39.8	1200 milk, 50 meat-powder.	1002	13.61	42	54	19.76	2.13	21.89	8.28
39.9	1500 milk.	1020	8.0	52	67	15.86	2.13	18.02	10.02

It will be noted that there was a large loss of body nitrogen on every day of the experiment. Even when the diet contained 25.1 grams of nitrogen, the excreta of the day contained 31.5 grams, indicating a loss of 6.4 grams from the body. The days of the smallest loss of tissue nitrogen were those on which the largest quantity (90 grams) of carbohydrates was given. Also a diet containing 17.85 grams of nitrogen seems to protect the proteid waste about as well as one with 25.1 grams of nitrogen, when both diets contain equal quantities of carbohydrates and fat.

Von Leyden and Klemperer regard the above experiment as indicating the advantage of a large proteid ingestion in preventing tissue waste. But deficient calorific value and lack of carbohydrates may be accountable for the increased waste on the lower proteid diets. It must also be remembered that proteid itself yields carbohydrate in metabolism. That carbohydrates of themselves cannot prevent the toxic waste of proteid tissue is beautifully illustrated in another experiment given by the same authors. The case was again one of typhoid, and carbohydrates were given in large quantity:

METABOLISM IN ABDOMINAL TYPHOID. DIET HIGH IN CARBOHYDRATE.

Highest Temp.	Food.					Excreta.		
	Quantity in Grams.	Calories.	N in Grams.	Fat in Grams.	Carb. in Grams.	Urine N in Grams.	Feces N in Grams.	Loss of Body N in Grams.
39.8	2808 milk, 400 lactose, 60 glucose, ⅐ liter sherry.	3020	14.9	98	386	20.1	1.5	6.7
39.7	2768 milk, 200 lactose, 133 glucose, ⅐ liter sherry.	3295	14.6	96	457	19.7	1.5	6.6
38.8	2460 milk, 300 lactose, ⅐ liter sherry.	2952	13.0	86	411	23.7	1.3	12.0
40.2	2366 milk, 300 lactose, ⅐ liter sherry.	2892	12.5	83	406	23.3	1.2	12.0
39.6	2430 milk, 109 lactose, ⅐ liter sherry.	2522	12.8	85	310	23.7	1.3	12.2
38.8	2080 milk, 200 glucose, ⅐ liter sherry.	2420	11.1	80	303	21.8	1.1	11.8
39.2	1870 milk, 200 glucose, ⅐ liter sherry.	2141	9.9	65	344	19.4	1.0	9.5

In this case it is definitely shown that a moderate amount of proteid, combined with a large quantity of fat and carbohydrates of large energy content, does not in any way prevent the constant waste of body tissue in typhoid fever. Since it has been demonstrated that carbohydrates prevent tissue destruction due to hyperthermia, it must be assumed that the nitrogen waste is here due to toxic destruction of the cells. An important question and one unanswered is this: Would the tissue waste have been less had more proteid been given? To this vitally significant question there is to-day no answer. If the tissue waste on this diet is an inevitable consequence of the disease and is not to be prevented by increasing the proteid in the food, then such proteid increase is to be avoided on account of its extra heat-producing power,—its specific dynamic action.

An illustration of the course of nitrogen metabolism in a different fever—namely, pneumonia—may also be taken from von Leyden and Klemperer. The details are as follows:

METABOLISM IN PNEUMONIA.

Temp. on Successive Days.	Food.					Excreta.			Loss of Body N.
	Quantity in Grams.	Calories.	N.	Fat.	Carbo-hydrates.	Urine N.	Feces N.	Total N.	
40.8 (highest).	2000 milk.	1360	10.6	70	90	24.7	0.9	25.6	15.0
40.9 (highest).	2000 milk, 150 cream, 100 lactose.	1980	11.4	85	197	22.8	0.9	23.7	12.3
41.2 at 12 M. 36.8 at 7 P. M.	2000 milk, 150 lactose.	1975	10.6	70	240	21.7	0.9	22.6	12.0
37.3 (highest).	2000 milk, 200 cream.	1612	11.7	90	99	21.9	1.1	23.0	11.3
36.8 (highest).	2000 milk, 200 cream, 2 eggs.	1752	13.7	100	99	18.5	1.1	19.6	5.9
36.8 (highest).	2000 milk, 300 cream, 4 eggs.	2018	17.3	120	104	18.7	1.1	19.8	2.5

In the above case it is again demonstrated that nitrogen equilibrium cannot be obtained during high fever, and also that the loss of body nitrogen does not cease at the crisis, but rather continues on account of the epicritical elimination of nitrogen derived from the proteid of the croupous exudate. During the time of this epicritical elimination the body appears unable to add new proteid to itself. About four days after the crisis, true convalescence begins with the upbuilding of new proteid tissue. (For further details regarding nutrition in fever the reader is referred to von Leyden and Klemperer's admirable article, from which the tables above have been transcribed.)

On autopsy of patients who have died of fevers, parenchymatous and fatty degeneration of the organs have been found. These changes have been ascribed to overheating of the cells.

Litten[1] warmed guinea-pigs artificially and noted fatty but no parenchymatous degeneration of the tissues. The space in which the animals were kept was, however, insufficiently ventilated, and the fatty change might have been caused by dyspnea, as results in normal animals (p. 215).

Naunyn[2] observed that rabbits might be artificially warmed for thirteen days so that an average body temperature of 41.5° was maintained without any parenchymatous or fatty degeneration taking place. The animals were supplied with ample food, water and a sufficient supply of air. Naunyn found that the red blood-cells of rabbits and dogs remained intact even at a body temperature of 42°. Welch[3] noticed fatty but no parenchymatous change in the tissues of rabbits after exposure to high temperature for at least a week. One rabbit which had been subjected to high temperature for four days was inoculated with the bacilli of the swine plague and died in thirty-six hours showing extreme fatty changes in the heart and other organs.

Ziegler[4] discovered degenerative changes, both parenchymatous and fatty, on artificially warming rabbits. The experiment was continued in one case for twenty-nine days. He however found a great reduction (30 per cent. and more) in the quantity of hemoglobin in his rabbits. It may well be a question whether the fatty change noticed in the liver and muscles was not due to anemia instead of to the hyperthermia. Since fatty infiltration is known to be caused by dyspnea, which frequently terminates life in fever, one might investigate this subject to see whether parenchymatous change in fever is not solely due to the toxins, and fatty change to the anaërobic cleavage of materials in the cells, which always induces fatty infiltration (p. 246).

As regards the etiology of fever, various attempts have been

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[1] Litten: "Virchow's Archiv," 1877, Bd. lxx, p. 10.

[2] Naunyn: "Archiv für ex. Path. und Pharm.," 1884, Bd. xviii, p. 49.

[3] Welch: "Medical News," 1888, vol. lii, p. 403.

[4] Ziegler: "Kongress für innere Medizin," 1895, Bd. xiii, p. 345.

made to identify a single factor which would cause the high temperature.

Krehl and Mathes[1] find that human urine during fever contains an increased quantity of albumoses which have been shown to possess a decidedly toxic action when introduced into animals. Klemperer[2] denies that these albumoses have any toxic action, and asserts that the results were due to impurities in preparation. In other respects the urine has generally been found to be of normal character. Thus Mohr[3] finds that the relation C to N in the urine is unchanged from the normal, which indicates that there is no qualitative change in the character of the general proteid metabolism.

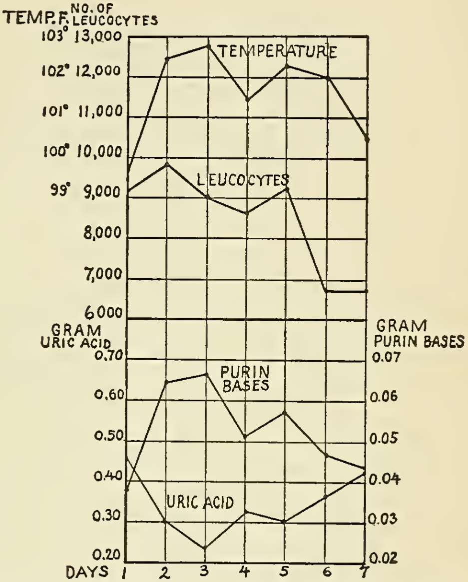

Fig. 10.—Resection of knee-joint for tubercular arthritis.

However, there is a very noteworthy record made by A. R. Mandel[4] that the rise of temperature in aseptic or surgical fevers is accompanied by a large increase in the purin bases in the urine of patients fed with milk. The temperature rises and falls with the quantity of purin bases eliminated. The uric acid elimination is reduced

[1] Krehl and Mathes: "Archiv für klinische Medizin," 1895, Bd. liv, p. 501.

[2] Klemperer: "Naturforscherversammlung," 1903, 2, ii, p. 67.

[3] Mohr: "Zeitschrift für klinische Medizin," 1904, Bd. lii, p. 371.

[4] Mandel: "American Journal of Physiology," 1904, vol. x, p. 452.

(p. 279). These relations are illustrated in Fig. 10,—a case of resection of the knee-joint for tubercular arthritis.

That the purin bases can be the cause of the rise of temperature is indicated by the experiments of Burian and Schur[1] who found that when nucleoproteid was administered intravenously to a dog, a rise of temperature followed. Mandel showed that a subcutaneous injection of forty milligrams of xanthin caused a marked rise in the temperature of a monkey, and that the administration of a strong decoction of 60 grams of coffee (containing trimethyl-xanthin) to a man unused to coffee drinking, was followed by a febrile temperature. This is shown in Fig. 11.

Another research available in this connection is that of von Jacksch,[2] who noted that the purin bodies in the urine of tuberculous patients may increase from a normal equivalent of 4.4 per cent. of the total nitrogen excreted, to one representing 11.3, or even 17.39 per cent. Also Benjamin[3] reports a case of typhoid whose urine contained the large quantity of 0.1 gram of purin bases with 0.54 gram of uric acid. Such results indicate abnormal tissue destruction, and Mandel believes that the purin bases liberated through the toxic destruction of tissue would have a considerable effect in producing the temperatures discovered.

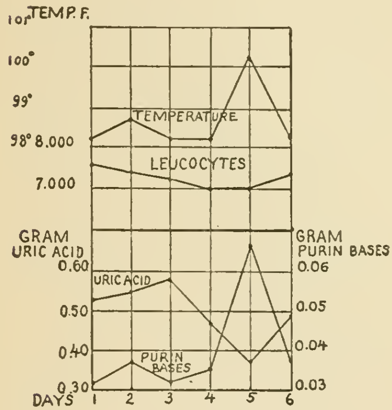

FIG. 11.—Case A. M. Given decoction of 60 gms. coffee.

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[1] Burian and Schur: "Pflüger's Archiv," 1901, Bd. lxxxvii, p. 239.

[2] Von Jacksch: "Zeitschrift für klinische Medizin," 1902, Bd. xlvii, p. 1.

[3] Benjamin: "Salkowski's Festschrift," 1904, p. 61.

It would indeed be a most striking fact if it should be found that the cause of the febrile temperature lay in the effect of purin bases on the heat-regulating apparatus of the mid-brain acting through the vasomotor system. Antipyretics do not lower body temperature in the normal organism in man. Is their action merely to nullify the activity of purin bases upon the nerve centers? Future research alone can decide this. An unpublished work by Mandel in the writer's laboratory seems to show that this is the mode of action in the case of salicylic acid. Perhaps such conjectures are out of place in a book of this sort, but they simply emphasize the extraordinary field which lies open to the investigator in clinical medicine.

CHAPTER XIV.

PURIN METABOLISM.—GOUT.

Uric acid was discovered in urinary calculi by Scheele in 1776, and was found to be present in gouty concretions by Wollaston in 1797. It has since been the subject of investigations almost without number, and of theoretical speculation beyond that of any other chemical substance described in medical literature. The older work concerning the excretion of uric acid is almost valueless on account of the inadequacy of the chemical methods of the times. Accurate determinations of uric acid date from the introduction of a new method of analysis by Salkowski in 1882.

The newer researches are also based on more exact chemical knowledge of the precursors of uric acid. Much valuable information has been gathered as regards the normal method of production of uric acid, although it will be seen that on the pathological side there is little beyond the conjectural to reward the student.

Emil Fischer[1] grouped together uric acid, hypoxanthin, xanthin, adenin and guanin as bodies whose varying structure depended upon slight changes around the chemical nucleus of a substance called purin. Purin, according to Fischer, may occur in the body, but on account of its ready decomposability, has not been discovered there.

The relations between the purin bodies may be judged from the following formulæ:

Purin	$C_5H_4N_4$
Hypoxanthin	$C_5H_4N_4O$
Xanthin	$C_5H_4N_4O_2$
Uric acid	$C_5H_4N_4O_3$
Adenin	$C_5H_3N_4NH_2$
Guanin	$C_5H_3N_4ONH_2$

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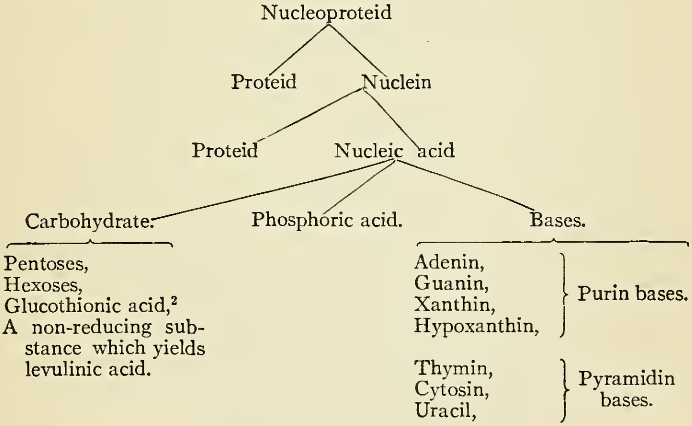
[1] Fischer: "Berichte der deutschen chemischen Gesellschaft," 1899, Bd. xxxii, p. 435.

Hypoxanthin, xanthin, and uric acid are respectively mono-, di-, and tri-oxypurin. Adenin is aminopurin, and guanin is aminohypoxanthin. It is evident that uric acid is the most highly oxidized product of the series, and might readily arise from the oxidation of hypoxanthin and xanthin. It is also apparent that by supplanting the NH_2 group in adenin and guanin by O, they would be converted into hypoxanthin and xanthin respectively, and that from these substances uric acid might arise through further oxidation.

For greater detail of the chemistry of purins, the reader is referred to any text-book on physiological chemistry.[1] The four precursors of uric acid, hypoxanthin, xanthin, adenin, and guanin are collectively called the *purin bases.* The general term, *purin bodies*, includes uric acid also.

Since Salomon discovered, in 1880, that purin bases exist in the nucleins which are present in the nuclei of cells, a great deal of work has been done to explain the chemical nature of these nuclear constituents. A summary of the products which can be obtained from nucleoproteids is as follows:



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[1] Consult also Mendel: "The Formation of Uric Acid," Harvey Society Lecture, "Journal of the American Medical Association," 1906, vol. xlvi, p. 843.

[2] Mandel and Levene: "Zeitschrift für physiologische Chemie," 1906, Bd. xlvii, p. 151.

Kossel and Steudel[1] point out the fact that the purin bases contain the pyramidin nucleus, and that cytosin, for example, needs only cyanic acid, CONH, and an atom of oxygen, to convert it into uric acid.

They query whether the pyramidin bases are precursors or metabolized products of the purins.

Horbaczewski[2] was the first to note that the ingestion of nucleins largely increased the uric acid in the urine. Food free from nuclein has not this effect. He also found that if fresh spleen pulp, which contains no uncombined purin bases, be permitted to putrefy, xanthin and hypoxanthin made their appearance. If now the pulp was shaken in the air, uric acid was formed from the oxidation of the bases.

Spitzer[3] found that when air was passed through aqueous extracts of spleen and liver digested at 40° and with exclusion of putrefaction, uric acid was produced. The quantity of purin bases present decreased with the increased formation of uric acid. Purin bases added to such a digest were converted into uric acid, hypoxanthin and xanthin readily and almost completely, and guanin and adenin with greater difficulty. This work established the presence of oxidizing enzymes, the xanthin oxidazes, which could act on the purin bases in the organism converting them into uric acid.

Minkowski[4] has shown that if a man be given hypoxanthin, the quantity of uric acid increases in his urine. He also showed that if a man ingest thymus gland, the nuclein of which yields principally adenin, the amount of uric acid is increased in the urine. If the thymus be given to a dog, the uric acid plus allantoin elimination is increased. Allantoin is an oxidation product of uric acid more frequently found in dog's than in human urine. Minkowski discovered finally that adenin, when administered to a dog, did not increase the uric acid elimination,

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[1] Kossel and Steudel: "Zeitschrift für Physiologie," 1903, Bd. xxxviii, p. 49.

[2] Horbaczewski: "Sitzungsberichte der Wiener Academie der Wissenschaft," 1891, Bd. c, Abth. iii, p. 13.

[3] Spitzer: "Pflüger's Archiv," 1899, Bd. lxxvi, p. 192.

[4] Minkowski: "Archiv für ex. Path. und Pharm.," 1898, Bd. xli, p. 375.

and was not excreted as such, but on autopsy of the dog the uriniferous tubules were found to contain crystals the chemical structure of which showed them to be aminodioxypurin. In other words, adenin administered combined in nucleic acid loses its amino (NH_2) group, receives three atoms of oxgyen, and is thereby converted into uric acid; adenin administered as such receives two atoms of oxygen but does not lose its NH_2 group at the point for the attachment of the third atom of oxygen. This work attests a varying behavior of purin bodies in accordance with their method of chemical union with other substances, and offers a suggestive key to certain relations observed in gout (p. 284). When theophyllin, caffein, and theobromin, the methylated purins found in tea, coffee, and cocoa, are ingested they are not oxidized to uric acid, but they increase the purin bases in the urine.[1]

The original investigations of Horbaczewski have recently been considerably extended by Schittenhelm and by Walter Jones, especially in regard to their explanation along lines of enzymotic activity.

Jones and Partridge[2] find that although the great majority of the organs of the body, when self-digested at 40° (autolysis), convert guanin and adenin into xanthin and hypoxanthin, presumably through the action of enzymes, extracts of the spleen of the pig cannot convert guanin into xanthin, although they can convert adenin into hypoxanthin. Jones therefore concludes that an enzyme, guanase, which normally removes the NH_2 group and replaces it with O, is wanting in the pig's spleen, while adenase, the enzyme acting on adenin in a similar fashion, is present there. Such a reaction would read:

$$\underset{\text{Adenin.}}{C_5H_3N_4NH_2} + H_2O = \underset{\text{Hypoxanthin.}}{C_5H_4N_4O} + NH_3$$

Investigating the subject further, the authors found that the

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[1] Krüger and Schmid: "Zeitschrift für physiologische Chemie," 1901, Bd. xxxii, p. 104.

[2] Jones and Partridge: *Ibid.*, 1904, Bd. xlii, p. 343; see also Levene: "American Journal of Physiology," 1904, vol. xii, p. 276.

pancreas contained the enzyme, guanase, which converts guanin into xanthin.

Sir Lauder Brunton[1] says that Stockvis, of Amsterdam, in 1860, found that crushed tissue had the power to destroy uric acid. This question has recently come into prominence and it has been shown that different organs have different powers in this regard, and that the same organ in animals of different species may behave quite differently.

Ascoli[2] found that crushed dog's liver had the power to destroy uric acid.

Wiener[3] showed that dog's liver and pig's liver destroyed uric acid, whereas calf's liver had less power to do so, or none at all. The kidney pulp of various animals also destroyed uric acid.

Schittenhelm[4] finds that in cattle the spleen, lungs, liver, intestine and kidney have the power of converting purin bases into uric acid in the presence of a constant oxygen supply. He finds a complete transformation of adenin, as follows: adenin, hypoxanthin, xanthin, uric acid. Guanin in like manner becomes xanthin and this again is converted into uric acid. He finds also that extracts of the spleen, intestines and lungs have no power to destroy uric acid as formed within them, but that the kidney, muscle, and liver extracts possess the power to destroy the new-formed uric acid.

Schittenhelm[5] in another paper finds that kidney extracts from cattle, through which oxygen is passed, may completely destroy uric acid through a uricolytic enzyme.

It has been shown by Pfeiffer[6] that the pulps of human kidneys and pigs' kidneys have the power to destroy uric acid completely, while dogs' kidneys have only a limited capacity in this regard.

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[1] Lauder Brunton: "Centralblatt für Physiologie," 1905, Bd. xix, p. 5.

[2] Ascoli: "Pflüger's Archiv," 1898, Bd. lxxii, p. 340.

[3] Wiener: "Archiv für ex. Path. und Pharm.," 1899, Bd. xlii, p. 375.

[4] Schittenhelm: "Zeitschrift für physiologische Chemie," 1905, Bd. xlv, p. 145.

[5] Schittenhelm: *Ibid.*, 1905, Bd. xlv, p. 161.

[6] Pfeiffer: "Hofmeister's Beiträge," 1905, Bd. vii, p. 463.

Almagia[1] finds that in the horse the greatest power of uric acid destruction is possessed by the liver, and then follow in order of diminishing activity the kidney, lymphatic glands, leukocytes, muscles, bone-marrow, spleen, and thyroid. In other organs, like the brain and the pancreas, the conditions are such as indicate a non-destruction of uric acid, which is produced by the oxidation of purin bases within them. Whenever uric acid was destroyed in the above experiments, Almagia found that glyoxylic acid (HOOC-CHO) was always present in the extract.

Summarizing these results it may be said that nuclein may be broken up by nuclease, a ferment found in all tissue. On the liberation of the purin bases, guanin and adenin are denitrogenized by guanase and adenase wherever these enzymes are found. Oxidizing enzymes, the xanthin oxidazes, now convert hypoxanthin and xanthin into uric acid, while a uricolytic ferment of varying potency in different tissues and in different animals may break up and destroy the uric acid. That processes akin to these go on within the living organs of the body is now generally believed, and the following animal experiments tend to confirm this doctrine, although it will become evident that the uricolytic power of kidney extracts, so frequently mentioned above, appears to be entirely overshadowed in the living kidney by the function of uric acid elimination.

It has already been stated that the ingestion of hypoxanthin by a man increased the uric acid output in the urine. It has long been known that if uric acid be given per os, or subcutaneously, it may in greater part be converted into urea, and in part eliminated in the urine. The quantity eliminated varies in different animals. Salkowski[2] finds that uric acid given to dogs is mostly eliminated as urea, although 17.7 per cent. appears in the urine in the form of allantoin. When uric acid is given to rabbits the urine contains urea, allantoin and some

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[1] Almagia: "Hofmeister's Beiträge," 1905, Bd. vii, p. 459.

[2] Salkowski: "Zeitschrift für physiologische Chemie," 1902, Bd. xxxv, p. 495.

uric acid. Mendel and White[1] found that allantoin was eliminated in the urine of cats and dogs after intravenous injection of urates. It is thus apparent that uric acid is readily destroyed in these animals and only a small quantity of a first oxidation product, allantoin, appears in the urine. Allantoin is not normally found in human urine. Glyoxylic acid, which has already been mentioned as constantly found when uric acid is destroyed in autolyzing tissue, is a substance which may be produced by treating allantoin with alkali. It has also been found in the urine of rabbits after intraperitoneal injection of from 2 to 5 grams of uric acid, and it has been detected in the urine of a gouty patient.[2]

Schittenhelm and Bendix[3] have injected rabbits subcutaneously and intravenously with guanin, and have found uric acid in greatly increased quantity in the urine, together with xanthin, which is normally absent in rabbits. The experiment indicates the metabolism of guanin *intra-vitam*, according to processes already observed *in vitreo*. If an Eck fistula, which excludes the portal blood from the liver, be made in a dog, uric acid appears in considerable quantity in the urine, which indicates that uric acid is normally oxidized in the dog's liver.[4]

Burian and Schur,[5] after careful perusal of the literature and of their own work, came to the conclusion that each variety of animal had a specific capacity for burning purin bodies ingested. They found a constant elimination in dog's urine of one-twentieth part of the purins ingested, one-sixth part in the case of rabbits, and one-half in the case of man. They describe how Minkowski, after giving a man hypoxanthin, saw that 48.6 per cent. of it was eliminated as uric acid; how Burian

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[1] Mendel and White: "American Journal of Physiology," 1904, vol. xii, p. 85.

[2] Almagia: *Loc. cit.*

[3] Schittenhelm and Bendix: "Zeitschrift für physiologische Chemie," 1905, Bd. xliii, p. 365.

[4] Hahn, Massen, Nencki, and Pawlow: "Archiv für ex. Path. und Pharm.," 1893, Bd. xxxii, p. 191.

[5] Burian and Schur: "Pflüger's Archiv," 1901, Bd. lxxxvii, p. 239.

repeated the experiment with the result that 46.2 per cent. appeared as uric acid; how the subject of the last experiment eliminated 51.1 and 53.8 per cent. of the purins contained in a meat diet, and 52.6 and 52.9 per cent. of those contained respectively in calf's liver and calf's spleen. Therefore, Burian and Schur multiplied the purin excretion of a man by two and of a dog by twenty in order to determine the total purin metabolism. They called these numbers the *integral factors* of purin excretion. The cause of the size of the integral factor will be discussed later.

It has been made clear that the purin bodies may be derived from ingested nucleins, but this cannot be the only source, since purins are found in the urine during starvation and on a diet free from purins. This indicates a constant production of these substances in metabolism, it has been thought, through the destruction of cell nuclei. Uric acid and purin bases from this source have been termed *endogenous* by Burian and Schur, in contradistinction to those which are eliminated after the ingestion of nuclein-containing food which are called *exogenous*.

Burian and Schur[1] also established the fact that while the endogenous uric acid elimination varied between 0.3 and 0.6 grams daily, according to the individual, it did not vary in the same individual but was a constant factor of his metabolism.

A purin-free diet is obtained by giving such articles of food as milk, eggs, bread, potatoes, fats, and sugars, none of which contain nuclear material which forms exogenous purins in the body. Burian and Schur found that on such a diet the uric acid elimination was entirely independent of the quantity of proteid ingested. It has been demonstrated by Rockwood[2] that the endogenous uric acid elimination is independent of the calorific value of the diet. Addition of 500 calories contained in maple sugar to a diet containing 2500 calories did not affect the excretion of uric acid. Rockwood's experiments extended over a long period of time. His individuals were nourished on

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[1] Burian and Schur: *Loc. cit.*

[2] Rockwood: "American Journal of Physiology," 1904, vol. xii, p. 38.

milk, eggs, white bread, crackers, cheese, apples, and butter. The constancy of the uric acid output in the same individual is seen in the following table,—in one case the record covering nearly a year:

TABLE SHOWING THE CONSTANCY OF THE DAILY ENDOGENOUS URIC ACID EXCRETION IN THE SAME INDIVIDUAL (TWO SUBJECTS).

PERSON, A.	DATE, 1903.	N IN URINE, GRAMS.	URIC ACID, GRAMS.
	January	11.99	0.308
	February	11.58	0.305
	March	11.15	0.315
	May	12.63	0.321
	July	12.68	0.313
	November	9.99	0.298
PERSON, B.	January	13.41	0.478
	March	13.92	0.452

This total shows the constancy of the output of endogenous uric acid in the same individual during a long period. Here the difference in the behavior of two individuals might possibly be ascribed to a personal idiosyncrasy as regards the uricolytic power of the subject, or to a difference in the capacity of producing uric acid. From the record of Chittenden's[1] experiments, which covered a period of twenty-one months, it may be observed that a very low proteid diet and moderate intake of food were without effect on the output of uric acid.

Burian and Schur[2] have made a series of experiments as regards the cause of the "integral factor" of purin metabolism, which has already been defined. They find that a part of the endogenous purins are burned in metabolism, for the uric acid elimination in the dog rises largely after cutting the liver from the circulation by means of an Eck fistula. They note that no one has been able to find uric acid in normal blood. They desired to see if uric acid would accumulate in the blood if the kidneys were both extirpated. No such result followed nephrectomy in a dog. The purin bodies were apparently completely burned. They then extirpated the kidneys and ligated the

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[1] Chittenden: "Physiological Economy in Nutrition," 1904, p. 24.

[2] Burian and Schur: *Loc. cit.*

aorta at a point just above the celiac artery. The operation cut off the liver and intestine from the circulation. Under these circumstances uric acid accumulated in the blood because its destruction was not accomplished by the liver. The question arises: If the normal organism can completely destroy all purins, why should a definite fraction be continually eliminated in the urine? Burian and Schur believe that endogenous purins, formed in the tissues, are oxidized therein to uric acid, and in so far as this substance is carried to such organs as the liver, it is destroyed, but in so far as it passes through the renal arteries, it is removed by the kidney. In confirmation of this they show that a diuretic which increases the blood-flow to the kidney likewise increases the uric acid elimination, without affecting the other nitrogen constituents of the urine. Possibly the fall in uric acid elimination noted by Mandel in aseptic fever (p. 267, Fig. 10) may be similarly due to a constriction of the renal vessels which always accompanies fever.

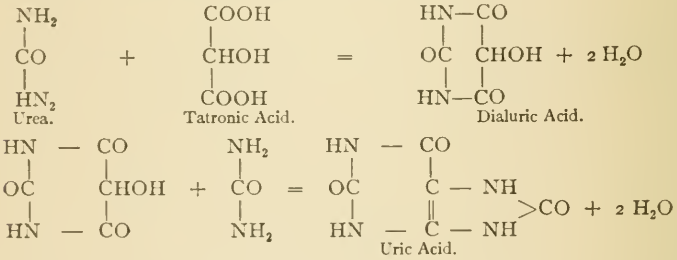
Burian and Schur conclude that of the mass of blood which receives uric acid from the tissues in man, the same amount flows through the organs which destroy uric acid as flows through the kidney, and hence the integral factor of two. On the other hand, the relation between the volume of kidney blood and the volume of blood passing through the organs which destroy uric acid in dogs, must be as 1:20 in order to explain the integral factor twenty. At first sight this does not explain why exogenous purins, which must pass from the intestine to the dog's liver, should escape complete destruction in that organ. Burian and Schur, however, have shown that whereas uric acid given *per os* is almost completely destroyed in the dog, the purin bases or nuclein digestive products containing them apparently pass through the liver to be oxidized to uric acid elsewhere.

The liver has the power of oxidizing uric acid but not the bases. Hence the behavior of exogenous purins must be exactly the same as if they arose in the general metabolism of the tissues themselves and were oxidized to uric acid, which was then carried in definite fractions, in accordance with the relative volume of the blood supply, either to the kidney for elimination or to the organs where uric acid is destroyed.

This explanation of the cause of the integral factor would explain the results of Loewi,[1] which showed that the ingestion of the same amount of nuclein-containing food by different people resulted in the excretion of the same increased quantity of uric acid in the urine.

The source of the endogenous purins has been the cause of considerable speculation. In birds there is a large synthetic production of uric acid in the liver, for Minkowski[2] has shown that extirpation of the liver in geese leads to a replacement of uric acid by ammonia and lactic acid in the urine.

Wiener[3] has suggested that there is a synthetic formation of uric acid in the mammalian organism from urea and tatronic acid according to the following formulæ:



$$\begin{array}{c} NH_2 \\ | \\ CO \\ | \\ HN_2 \end{array} + \begin{array}{c} COOH \\ | \\ CHOH \\ | \\ COOH \end{array} = \begin{array}{l} HN-CO \\ |\quad\;\; | \\ OC\;\; CHOH \\ |\quad\;\; | \\ HN-CO \end{array} + 2\,H_2O$$

$$\begin{array}{lcl} HN & - & CO \\ | & & | \\ OC & & CHOH \\ | & & | \\ HN & - & CO \end{array} + \begin{array}{c} NH_2 \\ | \\ CO \\ | \\ NH_2 \end{array} = \begin{array}{lcl} HN & - & CO \\ | & & | \\ OC & & C - NH \\ | & & \| \qquad\quad > CO \\ HN & - & C - NH \end{array} + 2\,H_2O$$

Burian,[4] however, has demolished this theory by showing that although tissue extracts when digested with either tatronic or dialuric acid oxidize xanthin to uric acid more readily than without them, still there is absolutely no formation of uric acid except from purin compounds present.

Ingestion of pyramidin bases (p. 272) has also failed to yield purins in the organism.[5]

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[1] Loewi: "Archiv für ex. Path. und Pharm.," 1900, Bd. xliv, p. 1.

[2] Minkowski: *Ibid.*, 1886, Bd. xxi, p. 41.

[3] Wiener: "Hofmeister's Beiträge," 1902, Bd. ii, p. 42.

[4] Burian: "Zeitschrift für physiologische Chemie," 1905, Bd. xliii, p. 526.

[5] Steudel: *Ibid.*, 1903, Bd. xxxix, p. 136.

Burian[1] has investigated the source of the endogenous purins and comes to the conclusion that only a small part of the endogenous uric acid arises from the nucleo-proteids of cellular tissue or those of dead leukocytes. It would require too large a destruction of tissue to provide from 0.3 to 0.6 gram uric acid or 0.1 to 0.2 gram purin nitrogen daily in the urine if it all arose from cell nuclein.

Burian and Schur's[2] analyses, showing the content of purin nitrogen in various tissues, is given below:

TABLE SHOWING THE QUANTITY OF PURIN N CONTAINED IN 100 GRAMS OF DIFFERENT ANIMAL TISSUES.

	Total Purin N.	N in Free Purin Bases.
Meat	0.06	0.045
Thymus	0.45	0.05
Calf's liver	0.12	0.033
Calf's spleen	0.16	0.046

To obtain the amount of endogenous uric acid present in the urine, if it were produced by the destruction of nucleo-proteids, it would be necessary to completely destroy nuclein to the extent of that contained in more than 100 grams of liver. It does not seem possible that nuclein destruction or nuclein metabolism could reach this extent.

The experiments of Burian[3] consisted in perfusing dog's muscles with blood free from uric acid. He noticed that after the perfusion of such blood through the muscles, uric acid was constantly found in it. If the muscle was caused to contract during the perfusion, a very considerable increase in the quantity of the purin bases was found in the blood and there was an increase in the quantity of these bases found in the muscles themselves.

Burian concludes that in the resting muscle there is a constant production of hypoxanthin which is converted into uric acid through the activity of the xanthin oxidase. In the active muscle there is a greater production of hypoxanthin which is not completely oxidized on account of a local oxygen deficiency.

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[1] Burian: "Pfluger's Archiv," 1905, Bd. xliii, p. 532.

[2] Burian and Schur: *Ibid.*, 1900, Bd. lxxx, p. 308.

[3] Burian: *Loc. cit.*

It had been found by many previous observers that exercise has no effect on the purin excretion in the urine of twenty-four hours in man. Burian, however, finds a large increase in the purin elimination for an hour of two after severe muscular exercise, and this is followed by a compensatory reduction in the output during those subsequent hours which represent the interval of weariness in the muscle.

These observations were confirmed by the work of Rockwood,[1] who saw that the purin excretion was less during the night than during the day, and by the work of Pfeil,[2] who found a constant morning rise in the output of purins in human urine.

These facts confirm Burian's contention that the most general source of endogenous purins is a constant production of hypoxanthin in muscle, a production which varies with the individual and is possibly proportional to the mass of his musculature. Comparable to this is the constant production of creatin (p. 118). Hypoxanthin is oxidized to uric acid in the muscle, and uric acid, if carried to the liver, which is certainly the principal organ for its destruction, may there be oxidized. Such of the purin bases as escape oxidation may be excreted by the blood flowing through the kidney, even as uric acid is excreted under the same circumstances.

Just as the whole trouble in diabetes turns upon the inability of the organism to destroy sugar, so the symptoms manifested in gout are dependent upon the deposit of acid urate of sodium in certain localities. One of the earliest descriptions of gout comes from Sydenham, who suffered for forty years from the disease and published an extended account of it in 1683. It was Garrod[3] who first established the fact that uric acid was present in the blood of gouty persons. He believed that this excess of urate was the cause of gout, the excess being deposited from the blood in the joints in the form of crystals. The problem of metabolism in gout is a problem of the fac-

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[1] Rockwood: *Loc. cit.*

[2] Pfeil: "Zeitschrift für physiologische Chemie," 1904, Bd. xl, p. 1.

[3] Garrod: "The Nature and Treatment of Gout," 1859.

tors entering into the cause of this deposit of urate. The general metabolism, exclusive of the purin factor, is exactly the same as in health. Magnus-Levy[1] proved that the oxygen absorption and carbon dioxid elimination is the same in gout as in health. The cause of the trouble must be sought elsewhere than in a reduced general oxidation power of the tissues.

Clinical experience teaches that the predisposing causes are excessive eating, little muscular exercise, the abuse of alcoholic beverages, and lead-poisoning.

Beebe[2] has administered alcohol in various forms to a normal individual. He finds that even large doses have no effect on the hourly excretion of uric acid in a fasting man. The endogenous purin metabolism is therefore unchanged by the ingestion of alcohol. It is important to know that alcohol is apparently without effect upon such part of the purins as may be directly derived from cell metabolism. On the other hand, when alcohol is given with nuclein-containing food, the uric acid elimination rises markedly. It was found that port wine was more potent in this regard than a larger quantity of alcohol taken in a purer form. The addition of 350 c.c. of port wine on two successive days to a mixed diet which had been constantly maintained for several days, caused a rise in uric acid elimination from 0.5 gram to 0.7 gram on the first day of port wine ingestion, and to 0.8 gram on the second day, while the following alcohol-free day showed an elimination of only 0.55 gram. Beebe ascribed this action to a reduction of uricolytic power in the liver.

Minkowski,[3] with a master hand, summarizes modern knowledge concerning gout as follows:

1. The deposit of urate in the tissues is the first evidence of the formation of the specific gouty nodules. These tissues are not necrotic, as taught by Ebstein.

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[1] Magnus-Levy: "Berliner klinische Wochenschrift," 1896, No. xix, p 416.

[2] Beebe: "American Journal of Physiology," 1904, vol. xii, p. 13.

[3] Minkowski: von Leyden's "Handbuch der Ernährungstherapie," 1904, Bd. ii, p. 277.

2. The tissue changes in the vicinity of the gouty nodules are in part due to mechanical, in part to chemical or osmotic action, caused by the precipitated urates.

3. The acute inflammation in gout, as observed during the attack, is produced in the vicinity of the urate deposits through some unknown cause. Traumatic, toxic, or infectious elements appear to be collectively active in this regard. The attack probably constitutes the reaction of the organism to rid itself of uric acid, an effect which is only partly realized.

4. An accumulation of uric acid in the blood is a constant accompaniment of gout.

5. The increased quantity of uric acid in the blood must not be considered as the cause of the precipitation of urates in the gouty nodules. There must be certain local influences which favor the deposit of urates; for Klemperer has shown that the blood of gouty patients may dissolve much more uric acid than is actually present in it; and again, the blood in leukemia may contain as much uric acid as in gout, without there being any indication of a deposit of urate.

6. The uric acid elimination is the same in the gouty as in the normal person, except at the time of the attack. Before the attack there is retention, but during and after the attack an increased excretion of uric acid in the urine.

7. The accumulation of uric acid in the blood is not due to a diminished oxidation of uric acid, but rather to a diminution in the quantity excreted in the urine.

8. It is not certain that the lessened excretion of uric acid is due to a disturbance of renal function. Very likely it depends upon the presence of uric acid in some abnormal chemical union. This abnormal substance may be with difficulty eliminated in the urine, but may lend itself readily to the formation of tophi (p. 273).

9. The ultimate cause of the unusual behavior of uric acid in gout is probably an abnormal metabolism within the nuclei of the cells, where the nucleic acid content is the means of solu-

tion and conveyance not only of the purin bases but also of uric acid.

The opinions of other modern workers vary somewhat from those of Minkowski, as appears in the following:

Almagia,[1] in Hofmeister's laboratory, has performed some interesting experiments and concludes that the older view of Garrod is correct,—that is, that an excess of urates in the blood is the cause of gout. Almagia finds that thin strips of cartilage suspended in dilute neutral solutions of sodium urate absorb the salt, do not destroy it, but cause it to be deposited in fine crystals within the cartilage. He furthermore injected five to seven grams of uric acid into the peritoneal cavity of rabbits, a dose which usually killed them. On testing the liver, spleen, muscles and lungs with the murexid test for uric acid, negative results were obtained, whereas cartilage gave a positive reaction indicating the presence of urates. Almagia concludes that the deposit of urates in the cartilage of a gouty patient is but the result of a temporary or permanent increase in the uric acid content of the blood.

The work of Soetbeer[2] is of the best modern character, and it confirms the older view of Garrod that the cause of gout is a retention of uric acid. Soetbeer compared the excretion of uric acid by gouty people during three-hour intervals with that of normal individuals, as observed by Pfeil (p. 282). In one case of long standing gout, of light character and with long intervals between the attacks, there was little variation from the normal in the uric acid excretion. In another case of gout, a patient who was examined between the attacks showed no increase in uric acid output after changing from a purin-free diet to one containing 320 grams of meat, and showed only a slight increase in elimination after 640 grams of meat were given. These results were obtained six weeks after the last attack and at a time when the patient was entirely free from pain. In still another case 350 grams of meat were given during the

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[1] Almagia: "Hofmeister's Beiträge," 1905, Bd. vii, p. 466.

[2] Soetbeer: "Zeitschrift für physiologische Chemie," 1904, Bd. xl, p. 54.

attack to a gouty patient who had no fever and whose urine was free from albumin and sugar. The results were as follows:

	Uric Acid in Grams.
Diet free from purins	0.276
Diet free from purins	0.328
Diet + 350 grams meat	0.316
" " " "	0.270
" " " "	0.255

In this experiment even during the days of purin-free diet there was no "morning rise" noted as a normal incident by Pfeil. The hourly uric acid excretion was very even. The kidney was apparently removing uric acid up to the limit of its capacity. This work renders it probable that uric acid retention is the cause of gout.

Von Noorden and Schliep[1] suggest that gouty patients be tested for their "tolerance" for purin bodies just as diabetics are tested for their tolerance for carbohydrates. Four hundred grams of meat contain 0.24 gram of purin nitrogen, of which in the normal person one-half is oxidized and one-half eliminated in the urine—0.24 gram N = 0.72 gram uric acid. A patient was put on a purin-free diet; was given 400 grams of meat, then put on a purin-free diet again, and afterwards was tested with 200 grams of meat. The results were as follows:

Day.	Diet.	Uric Acid in Grams.
4	Purin-free	0.462
5	" " + 400 g. meat	0.522
6	" " + 400 g. meat	0.544
7	" "	0.539
8	" "	0.528
9	" "	0.458
10	" " + 200 g. meat	0.549
11	" " + 200 g. meat	0.655
12	" "	0.647
13	" "	0.499
14	" "	0.433

The authors conclude that while the increased uric acid output after giving 400 grams of meat is not what it would be

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[1] Von Noorden and Schliep: "Berliner klinische Wochenschrift," 1905, Bd. xlii, p. 1297.

normally, yet after giving 200 grams the quantity of additional uric acid (which should amount to 0.18 gram) is fully eliminated. Hence this patient had a tolerance for the purins in 200 grams of meat.

Dietetic rules for gouty sufferers are intended to combat the fundamental anomalies of the metabolism. The organism must not be overloaded with uric acid. Minkowski's rules[1] for treatment of gout may be thus abstracted: Sweetbreads, liver, and kidney are to be rigidly excluded from the diet. Meat is to be taken in moderation only. Wine should be taken sparingly or not at all, and beer rigidly excluded on account of the nuclein in yeast. Cathartics may be given to rid the intestine of purin bodies excreted into the intestinal canal, and water drinking, which promotes a larger flow of urine and increased uric acid elimination, is strongly to be commended. The diet for a gouty patient should contain each day 100 or 120 grams of proteid, 80 or 100 grams of fat, and 250 or 300 grams of carbohydrates (2200 to 2600 calories). This should not include more than from 200 to 250 grams of meat per day. Indigestible cakes, pies, rich foods and heavy salads should be forbidden. Moderation and self-control are the watchwords for the gouty sufferer.

It is impossible to increase the oxidation of uric acid, and no treatment now known increases its solubility. Minkowski hopes that some organic compound may be discovered which will accomplish this purpose. He believes the relief given by preparations of the salicylate group is afforded only through their stopping pain and promoting perspiration.

Bearing the facts of the above discussion in mind, the reader will comprehend that present day doctrines concerning metabolism in gout may shortly become entirely obsolete through new and far-reaching discoveries.

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[1] Minkowski: "Deutsche medizinische Wochenschrift," 1905, Bd. xxxi, p. 409.

CHAPTER XV.

THEORIES OF METABOLISM AND GENERAL REVIEW.

There has been a difference of opinion as to whether the food substances must first become vital integers of the living cell, or whether the non-living food materials are metabolized without ever becoming a constituent part of the living protoplasm.

Pflüger held the former view,—that incorporation of nutritive matter with the living substance is essential to its metabolism. He conceived that living proteid may contain the labile cyanogen group in contrast with dead proteid which contains the amino group. He illustrated this by Wöhler's classic experiment of the easy conversion of ammonium cyanate into urea:

$$NH_4OCN = (HN_2)_2CO$$

Voit's theory was that the living proteid is comparatively stable and that food proteid which becomes the circulating proteid of the blood is carried to the cells and promptly metabolized. The other foodstuffs are also burned without first entering into the composition of the cell.

A mass of living cells composing the substance of a warm-blooded animal has the same requirement of energy as any similar mass of living cells composing the substance of any other animal of the same size and shape. The reason for the metabolism lies in unknown causes within the cells. Liebig conceived the cause to be due to the swinging motion of the small constituent particles of the cells themselves. If this hypothesis be accepted the vibrations of the cells may be assumed to shatter the proteid molecule into fragments consisting of amino bodies, and to break down fat and sugar into substances of a lower order than themselves.

The uniformity of the energy requirement is illustrated by the fact that the number of calories given off during the twenty-four hours by one square meter of surface, in various animals and in man in the condition of starvation, is the same.

Even in pathological conditions a remarkable constancy of total heat production is apparent. Thus, in such typical disturbances as anemia, diabetes, gout and obesity, the general laws governing the output of carbon dioxid, the absorption of oxygen and the production of heat, are found to be the same as in health. In fever the metabolism and heat production increase and this to a large extent on account of the warming of the cells. In exophthalmic goiter there is probably an increase in metabolism, due to the stimulus of an excessive production of iodothyrin in the thyroid gland, while in myxedema the absence of the same substance causes a considerable reduction in the metabolism. Drugs may influence the course of metabolism, iodothyrin increasing it and morphin profoundly diminishing it, but on the whole the most striking fact is not the variability, but rather the uniformity, of the processes concerned.

Within recent years the work of Kossel, Fischer, Hofmeister, Osborne and Levene has given a more definite conception of the composition of proteid than was before possible. There is every indication that the proteid molecule consists fundamentally of groups of amino fatty acids banded together. Proteids vary with the integral components of their chemical chains. It has long been known that the end products of tryptic digestion include such substances, but Kutscher first showed that continued tryptic digestion resulted in the almost complete transformation of proteid into these amino acids. Cohnheim discovered erepsin, an enzyme derived from the intestinal wall, which rapidly converts albumoses into these substances.

On chemical analysis, using methods developed in Emil Fischer's laboratory, the cleavage products of various proteids appear distributed as shown in the following table,[1] in which

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[1] Abderhalden, E.: "Zeitschr. f. physiol. Chem.," 1905, Bd. xliv, p. 17.

the figures given for globin represent the recovery of 70 per cent. of the constituents of its molecule:

COMPOSITION OF PROTEID.

	Casein.	Gelatin.	Elastin.	Globin from Hemoglobin.	Edestin.
Glycocoll	.0	16.5	25.75	.0	3.8
Alanin	0.9	0.8	0.58	4.19	3.6
Leucin	10.5	2.1	21.38	29.04	20.9
Pyrrolidin carboxylic acid	3.1	5.1	1.74	2.34	1.7
Phenylalanin	3.2	0.4	3.89	4.24	2.4
Glutamic acid	10.7	0.88	0.76	1.73	6.3
Aspartic acid	1.2	0.56	..	4.43	4.5
Cystin	0.065	.0	1.0	0.31	0.25
Serin	0.23	..	..	0.56	0.33
Oxy *a*-pyrrolidin carboxylic acid	0.25	3.0	..	1.04	2.0
Tyrosin	4.5	.0	0.34	1.33	2.13
Aminovalerianic acid	1.0	1.0	..	..	*
Lysin	5.80	2.75	..	4.28	2.0
Histidin	2.59	7.62	..	10.90	1.0
Arginin	4.84	0.40	0.3	5.42	11.7
Tryptophan	1.5	.0	..	*	*

* Present.

Proteid metabolism in plants and animals occurs in striking similarity to the changes brought about by enzymes and hydrolytic agents acting on proteid oustide of the tissues. Thus in the germinating seed Schultze[1] finds that asparagin, leucin, tyrosin, histidin, arginin and lysin arise from the metabolism of proteid. The occurrence of leucin and tyrosin in the liver and urine in such a diseased condition as phosphorus-poisoning has long been known, and Abderhalden and Bergell[2] report the presence of glycocoll in rabbit's urine after the administration of phosphorus. Urine after phosphorus-poisoning may also contain phenylalanin and arginin.[3] Wakeman[4] finds an altered quantitative relationship between histidin, arginin, and lysin

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[1] Schultze and Castero: "Zeitschr. f. physiol. Chemie," 1904, Bd. xliv, p. 455.

[2] Abderhalden and Bergell: *Ibid.*, 1903, Bd. xxxix, p. 464.

[3] Wolgemuth: *Ibid.*, 1905, Bd. xliv, p. 74.

[4] Wakeman: *Ibid.*, p. 333.

in the composition of liver substance after phosphorus-poisoning, arginin in particular being reduced below the quantity found in the liver of the normal dog. This possibly suggests a ready destruction of certain cell proteids rich in arginin which may be essential to vitality.

All forms of proteid decomposition follow, therefore, the pathway of cleavage into amino acids.

The life history of many of these substances has already been set forth in the preceding chapters, and it is here unnecessary to recapitulate.

The question arises, To what extent may the amino bodies formed within the intestine be regenerated into proteid? It is believed that the cells of the intestinal villus regenerate fat from fatty acid and glycerin, since neutral fat alone is found in the thoracic duct. But all the starch fed is not regenerated into starch, nor is maltose regenerated into maltose in the body. Much may be burned as dextrose and only a part is transformed into glycogen. Long ago Schultzen and Nencki[1] stated that a certain amount of amino bodies formed in digestive proteolysis was absorbed and burned, and that the absorbed proteid itself followed the lines of an enzymotic cleavage into amino bodies. In the light of newer knowledge several authorities have recently elaborated theories along similar lines. It has been pointed out by Folin[2] that there is little evidence of recontruction of all the proteid ingested. He cites the experiments of Nencki and Zaleski,[3] which showed that the portal blood during digestion contains four times as much ammonia as arterial blood, and that the mucosa of both stomach and intestine yield large quantities of ammonia. The inference is that the ammonia of the portal vein is derived from ammonia produced in the mucosa as well as from that which normally originates in the intestine during tryptic proteolysis.

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[1] Schultzen and Nencki: "Zeitschrift für Biologie," 1872, Bd. viii, p. 124.

[2] Folin: "American Journal of Physiology," 1905, vol. xiii, p. 117.

[3] Nencki and Zaleski: "Zeitschrift für physiologische Chemie" 1901, Bd. xxxiii, p. 206.

The existence of denitrogenizing enzymes is afforded by the example of the guanase and adenase of Walter Jones,[1] which respectively convert guanin into xanthin and adenin into hypoxanthin with the liberation of ammonia.

Folin believes that the greater part of the proteid ingested undergoes a denitrogenization through the hydrolysis of the amino cleavage products. Such a reaction would read

$$\equiv CNH_2 + H_2O = \equiv COH + NH_3$$

The ammonia may be converted into urea within the organism, and the nitrogen-free rest may be converted into sugar. The simplest expression of this is seen in the experiment of Neuberg and Langstein,[2] who found glycogen in the liver and lactic acid in the urine of a rabbit following the ingestion of alanin. The transformation of alanin into lactic acid may be written

$$\underset{\text{Alanin.}}{CH_3\,CHNH_2\,COOH} + H_2O = \underset{\text{Lactic Acid.}}{CH_3\,CHOH\,COOH} + NH_3$$

The conversion of lactic acid into sugar was demonstrated by the experiment of Embden and of A. R. Mandel, who showed increases in the sugar output in diabetes after the ingestion of lactic acid.

Wolf[3] finds that none of these amino substances has any effect on the blood pressure of animals so far as he has examined them. Abderhalden and Teruuchi[4] find that their nitrogen is in greater part converted into urea in the organism as well as that of artificially prepared peptids, such as glycyl-glycin.

Although some proteid metabolism may take place as above outlined, it is an undoubted fact that proteid may be synthesized in the body with the formation of new tissue, and also that proteids injected into the blood stream, as in cases of transfusion

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[1] Jones and Winternitz: "Zeitschrift für physiol. Chemie," 1905, Bd. xliv, p. 1.

[2] Neuberg and Langstein: "Archiv für Physiologie," Suppl. Bd., 1903, p. 514.

[3] Wolf: "Journal of Physiology," 1905, vol. xxxii, p. 171.

[4] Abderhalden and Teruuchi: "Zeitschrift für physiologische Chemie," 1906, Bd. xlvii, p. 159.

of blood serum, are rapidly destroyed and the nitrogen eliminated as urea. The conditions of proteid metabolism may, therefore, be entirely similar to those of starch metabolism: (1) digestive hydrolysis; (2) partial combustion of the end products; and (3) possible regeneration of portions of the end products into substances similar to the originals, but characteristic of the organism,—*i. e.*, glycogen and body proteids. In the case of proteids the second or metabolic process involves the partial passage of the end products through the glucose stage. The third or regenerative process is promoted by such a proteid as casein, which yields a large variety of cleavage products.

The chemical bases of such reconstruction is afforded by the artificial production of *peptids* by Emil Fischer, bodies which contain two or more amino acids united together. There are di,- tri,- and poly-peptids. For example, glycyl-glycin is formed by the union of two molecules of glycocoll with the loss of one of water, as follows:

$$\underset{\text{Glycocoll.}}{NH_2CH_2CO\ OH} + \underset{\text{Glycocoll.}}{HNHCH_2COOH} - H_2O =$$

$$\underset{\text{Glycyl-glycin.}}{NH_2\ CH_2\ CO\ NHCH_2\ COOH}$$

Kindred substances are alanyl-alanin, alanyl-glycin, leucyl-glycyl-glycin, dialanyl-cystin.[1] Their fate in metabolism is the same as that of proteid, and it is claimed that the presence of some of them is necessary for the proper synthesis of proteid in the organism (p. 105).

Folin[2] has discovered that a man fed with creatin-free food eliminates a constant quantity of creatinin nitrogen in the urine irrespective of the amount of nitrogen ingested with the food. Thus the urine of one man contained 16.8 grams of total nitrogen with 0.58 gram of creatinin nitrogen. The same man at another time, after large carbohydrate ingestion, eliminated 3.60 grams of total nitrogen and 0.60 gram of creatinin nitrogen. Folin conceives that the constancy of the creatinin and uric acid

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[1] Consult Abderhalden: "Lehrbuch der physiologischen Chemie," 1906.

[2] Folin: "American Journal of Physiology," 1905, vol. xiii, p. 66.

output is a true index to the necessary protoplasmic breakdown, and would define the nitrogen of such destruction as the endogenous nitrogen. To what extent, if any, urea nitrogen enters into this essential life metabolism he is not prepared to say. The same idea was expressed by Burian[1] in an article published ten days later than Folin's. Burian believes that purin bases are a constant product of muscle metabolism and that these are oxidized to uric acid, a part of which is further converted into urea. This process of itself would indirectly evolve urea as a constant product of the endogenous nitrogen metabolism. According to this newer conception the cells of the body through the swinging motion of their particles do continually break down their own protoplasm with the production of creatinin, purin bases, and perhaps other substances. These same cells may also break up exogenous amino radicles derived from ingested proteid or circulating proteid itself.

As regards fat metabolism Geelmuyden[2] is inclined to the opinion that oxybutyric acid, aceto-acetic acid and acetone are normal metabolism products derived from members higher up in the series.

Stoklasa[3] finds a ferment in animal tissues able to convert sugar into lactic acid. He quotes Oppenheimer's experiment, showing that whereas fresh normal blood yielded little acid on standing at 37°, much greater amounts were formed if dextrose were added. He believes that this lactic acid is subsequently converted into alcohol and carbon dioxid. He[4] describes the action of ferments as follows: *Lactalase* converts dextrose into lactic acid; *alcoholase* converts lactic acid into alcohol; *acetolase* converts alcohol into acetic acid: and, perhaps, *formilase* converts acetic into the unstable formic acid which yields methane.

Rubner[5] gives the following theory of metabolism: Living

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[1] Burian: "Zeitschrift für physiologische Chemie," 1905, Bd. xliii, p. 532.

[2] Geelmuyden: *Ibid.*, 1904, Bd. xli, p. 128.

[3] Stoklasa, Jelinek and Czerny: "Centralblatt für Physiologie," 1903, Bd. xvi, p. 712.

[4] Stoklasa: *Ibid.*, 1905, Bd. xviii, p. 793.

[5] Rubner: Von Leyden's "Handbuch der Ernährungstherapie," 1903, p. 78.

protoplasm, through the vibration of its particles, metabolizes the food substances. The action resembles catalysis. The energy liberated reacts on the particles of protoplasm, causing a change in their position and a cessation of metabolism. The particles then return to their original position and the cycle begins again. These processes require a fixed amount of energy. Rubner does not give his reasons for believing in this rhythm of excitation and rest.

The quantity of the combustion depends on the power of the cells to metabolize (Voit). In the resting state this metabolic power of the cells is influenced by the "law of skin area" (Rubner). Temperature (cooling or warming) and nerve excitation (muscle work, chemical regulation) affect the power of the cells to metabolize, perhaps through a variation in the capability of oscillation of the particles, an effect which is in turn maintained at the expense of the energy derived from metabolism. Living protoplasm metabolizes in accord with its necessities at the time, and never more. Large quantities of nutrient materials furnished will not increase cell metabolism. If food be ingested above the requirement for the organism, any excess will be retained in the body. The kind of metabolism depends upon the constitution of the fluid feeding the cells, whether proteid, carbohydrates or fats have been ingested.

Each ingested foodstuff exerts a specific dynamic action (Rubner). At a temperature of 33° the ingestion of the starvation requirement of energy in the form of fat increases the reqirement for energy 10 per cent., carbohydrate raises it 5 per cent., proteid 30 per cent. In other words, in the case of meat, in order to obtain calorific equilibrium about 140 calories must be ingested instead of 100, if that represents the starvation requirement. Rubner[1] explains that the cells of the body do not require more energy after meat ingestion than in starvation, but that the heat produced by a preliminary cleavage of proteid into dextrose on the one hand, and into a nitrogen-containing rest on the other, while yielding heat to the body does not furnish the

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[1] Rubner: "Gesetze des Energieverbrauchs," 1902, p. 380.

actual energy for the vital activities of the protoplasm. This is furnished principally by the dextrose derived from the proteid. Although it is necessary to abandon the older theory which pronounces glycogen (or dextrose) a direct cleavage product of proteid, still the explanation of Rubner remains tenable if interpreted in a newer light. If the energy requirement of the cell remains constant at 100, even after the ingestion of 140 calories of proteid, then 71.4 per cent. of the total heat value of the proteid is the quantity actually used for the vital processes. Since it has been shown in the writer's laboratory that meat proteid yields 58 per cent. of dextrose in metabolism, it may be calculated that 52.5 per cent. of the total energy of proteid may be available for the cells in the form of sugar. A balance of 19 per cent. must be obtained from other compounds, while 28.5 per cent. of the total heat value is wasted as heat without ever having been brought into the service of the life processes of the cells. Perhaps this 28.5 per cent. of heat loss represents the quantity produced by the cleavage of proteid into amino bodies and the denitrogenization of these radicles. (See p. 140.)

The constancy of the energy requirement in metabolism makes difficult the explanation of the action of the various ferments found in the body. These are of three varieties: hydrolytic, synthetic, and oxidizing, but these from the very principles of our knowledge must be subservient to the requirement of the living cells, and not themselves masters of the situation, as, for example, they become in the autolysis of dead tissue. It seems to be the requirement of the mechanism of cell activity which determines metabolism, and not primarily the action of enzymes, whose influence appears to be only intermediary.

Friedenthal[1] shows that proteid, colloidal carbohydrates, fats and soaps are not oxidizable in the cellular fluids without previous hydrolytic cleavage. After hydrolysis, however, the oxidases may effect an oxidation of the smaller molecules. The necessity of the hydrolytic ferment is also seen in the non-

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[1] Friedenthal: Verhandlungen der Berliner Physiologischen Gesellschaft, "Archiv für Physiologie," 1904, p. 371.

combustion of dextrose after the extirpation of the pancreas, the organ by which the ferment is supplied. Oxygen and the oxidases are present in ample quantity, but the sugar is not burned unless it be broken by its specific ferment. In the meantime the cell avails itself of a compensatory energy supply from other sources. It is impossible to apply anything similar to Ehrlich's side-chain theory to this condition of affairs, for the metabolism does not depend upon the satisfaction of chemical affinities, but rather upon a definite law of utilization of energy equivalents.

However clearly formulated the laws of metabolism may be, and many of them are as fixed and definite as are any laws of physics and chemistry, still the primary cause of metabolism remains a hidden secret of the living bioplasm.

APPENDIX.

TABLE SHOWING THE COST OF PROTEID AND ENERGY

As Furnished by a Number of Common Food Materials, at Prices Current in the Eastern Part of the United States.

Compiled by Langworthy, U. S. Department of Agriculture, 1905, in Farmers' Bulletin, No. 85, p. 19.

(1 pound = 453.6 grams.)

Kind of Food Material.	Price per Pound.	Cost of 1 Pound Proteid.	Cost of 1000 Calories Energy.	Amounts for 10 Cents.		
				Total Weight of Food Material.	Proteid.	Energy.
	Cents.	*Dollars.*	*Cents.*	*Lbs.*	*Lb.*	*Calories.*
Codfish, whole, fresh	10	0.90	48	1.000	0.111	209
Codfish, steaks	12	71	36	.833	.142	274
Bluefish	12	1.20	58	.833	.083	172
Halibut	18	1.18	40	.556	.085	253
Codfish, salt	7	.44	23	1.429	.229	437
Mackeral, salt	10	.61	10	1.000	.163	998
Salmon, canned	12	.62	18	.833	.162	547
Oysters (solids, 30 cents quart)	15	2.50	68	.667	.040	147
Oysters (solids, 60 cents quart)	30	5.00	136	.333	.020	74
Lobster	18	3.05	129	.556	.033	77
Beef, sirloin steak	25	1.52	26	.400	.066	380
Beef, sirloin steak	20	1.21	21	.500	.083	475
Beef, round	14	.74	16	.714	.136	615
Beef, stew meat	5	.38	5	2.000	.266	1,862
Beef, dried, chipped	25	.95	33	.400	.106	303
Mutton chops, loin	20	1.48	14	.500	.068	694
Mutton, leg	22	1.46	25	.454	.069	394
Pork, roast, loin	12	.90	10	.833	.112	1,016
Pork, smoked ham	22	1.55	14	.454	.064	729
Milk (7 cents quart)	3	1.06	11	2.857	.094	891
Milk (6 cents quart)	3	.91	10	3.333	.110	1,040
Wheat flour	3	.26	2	3.333	.380	5,363
Corn meal	2	.22	1	5.000	.460	8,055
Potatoes (90 cents bushel)	1½	.83	5	6.667	.120	2,020
Potatoes (45 cents bushel)	¾	.42	2	13.333	.240	4,040
Cabbage	2½	1.79	21	4.000	.056	484
Corn, canned	10	3.57	23	1.000	.028	444
Apples	1½	5.00	7	6.667	.020	1,420
Bananas	7	8.75	24	1.429	.011	414
Strawberries	7	7.78	42	1.429	.013	240

A more extensive compilation which permits not only the calculation of the nutritive value of the particular edible food but also of the approximate weight of inedible waste entailed in the direct purchase of the material in the market, is as follows:

COMPOSITION OF ORDINARY FOOD MATERIALS

According to Atwater and Bryant.

Report of the Storrs Agricultural Experiment Station, 1899, p. 113, somewhat abridged.

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
		Water	Unavailable Nutrients.	Available Nutrients.				
				Proteid.	Fat.	Carbohydrates.	Ash.	Fuel value per lb. = 453.6 Grams.
Animal Foods. *Beef (fresh).*	%	%	%	%	%	%	%	Calories.
Brisket	23.3	54.6	2.1	15.3	27.1	..	.7	1475
Chuck	16.3	62.7	1.8	17.9	17.1	..	.7	1095
Flank	10.2	60.2	1.9	18.3	19.9	..	.7	1225
Loin, lean	13.1	67.0	1.2	19.1	12.1	..	1.0	900
Loin, medium	13.3	60.6	1.8	17.9	19.2	..	.8	1185
Loin, fat	10.2	54.7	1.9	17.0	26.2	..	.9	1470
Neck	27.6	63.4	1.6	19.5	15.7	..	.7	1065
Plate	16.5	54.4	2.2	16.0	27.6	..	.6	1510
Ribs	20.8	55.5	2.0	17.0	25.3	..	.7	1430
Round, lean	8.1	70.0	1.0	20.7	7.5	..	1.1	735
Round, medium	7.2	65.5	1.6	19.7	12.9	..	.8	950
Round, fat	12.0	60.4	1.6	18.9	18.5	..	1.0	1175
Round, second cut	19.5	69.8	1.3	19.8	8.2	..	.8	750
Rump	20.7	56.7	2.0	16.9	24.2	..	.7	1380
Fore shank	36.9	67.9	1.4	19.8	11.0	..	.7	865
Tongue	26.5	70.8	1.3	18.3	8.7	..	.8	740
Shoulder and clod	16.4	68.3	1.5	19.0	10.7	..	.8	840
Fore quarter	18.7	60.4	1.8	17.4	20.3	..	.7	1220
Hind quarter	15.7	59.8	1.8	17.8	20.5	..	.7	1240
Side, lean	19.5	67.2	1.3	18.7	12.5	..	.9	910
Side, medium	17.4	59.7	1.8	17.6	20.9	..	.7	1250
Side, fat	13.2	47.8	2.5	15.7	34.6	..	.5	1805
Liver	7.0	71.2	1.2	20.4	4.3	1.7	1.2	620
Suet (unrendered tallow)	..	13.7	4.3	4.6	77.7	..	.2	3440
Hind Shank	53.9	67.8	1.4	20.3	10.9	..	.7	875
Beef (preserved and cooked).								
Dried and smoked	4.7	54.3	3.5	29.1	6.2	..	6.8	850
Brisket, corned	21.4	50.9	3.2	17.8	23.5	..	4.2	1370
Flank, corned	12.1	49.9	2.7	14.2	31.4	..	2.2	1635

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
		Water.	Unavailable Nutrients.	Available Nutrients.				
				Proteid.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
Animal Foods. *(Beef, preserved and cooked).*	%	%	%	%	%	%	%	Calories.
Plate, corned	14.5	40.1	3.7	13.3	39.8	..	3.5	1980
Rump, corned	6.0	58.1	2.2	14.8	22.1	..	2.8	1250
Canned, boiled	..	51.8	2.2	24.7	21.4	..	1.0	1415
Canned, corned	..	51.8	2.7	25.5	17.8	..	3.0	1275
Boiled beef (cut not given)	..	38.1	2.7	25.4	33.2	..	.7	1930
Roast, cooked	..	48.2	2.4	21.6	27.2	..	1.0	1410
Loin steak, cooked	..	54.8	2.0	22.8	19.4	..	.9	1290
Tripe, pickled	..	86.5	.6	11.3	1.1	..	.2	275
Veal (fresh).								
Breast	21.3	66.0	1.5	18.9	13.3	..	.8	950
Chuck	18.9	73.0	1.1	19.1	6.2	..	.8	650
Cutlets (round)	3.4	70.7	1.3	19.7	7.3	..	.8	710
Flank	..	68.9	1.3	19.9	9.9	..	.8	825
Leg	14.2	70.0	1.3	19.6	8.6	..	.9	760
Loin	16.5	69.0	1.3	19.3	10.3	..	.8	830
Neck	31.5	72.6	1.1	19.7	6.6	..	.8	680
Rib	24.3	72.7	1.2	20.1	5.8	..	.8	650
Shank	62.7	74.5	1.0	20.1	4.4	..	.8	590
Fore quarter	24.5	71.7	1.2	19.4	7.6	..	.7	715
Hind quarter	20.7	70.9	1.2	20.1	7.9	..	.8	740
Side	22.6	71.3	1.2	19.6	7.7	..	.8	725
Liver	..	73.0	.9	9.7	5.0	..	1.0	410
Lamb (fresh).								
Breast or chuck	19.1	56.2	2.0	18.5	22.4	..	.8	1335
Leg	17.4	63.9	1.7	18.6	15.7	..	.8	1050
Loin	14.8	53.1	2.2	18.1	26.9	..	.8	1520
Neck	17.7	56.7	1.9	17.2	23.6	..	.8	1360
Shoulder	20.3	51.8	2.2	17.6	28.2	..	.8	1565
Fore quarter	18.8	55.1	2.0	17.8	24.5	..	.8	1410
Hind quarter	15.7	60.9	1.8	19.0	18.1	..	.8	1160
Side	19.3	58.2	2.0	17.1	21.9	..	.8	1285
Lamb (cooked).								
Chops, broiled	13.5	47.6	2.5	21.0	28.4	..	1.0	1640
Leg, roast	..	67.1	1.4	19.1	12.1	..	.6	905
Mutton (fresh).								
Chuck	21.3	50.9	2.4	14.6	31.9	..	.7	1665
Flank	9.9	46.2	2.6	14.7	36.4	..	.5	1860

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
				Available Nutrients.				
		Water.	Unavailable Nutrients.	Proteid.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
Animal Foods.	%	%	%	%	%	%	%	Calories.
Mutton (fresh)								
Leg	18.4	62.8	1.7	17.9	17.1	..	.8	1095
Loin	16.0	50.2	2.4	1.55	31.4	..	.6	1660
Neck	27.4	58.1	2.0	16.4	23.4	..	.7	1335
Shoulder	22.5	61.9	1.7	17.2	18.9	..	.7	1160
Fore quarter	21.2	52.9	2.2	15.1	29.4	..	.7	1570
Hind quarter	17.2	54.8	2.1	16.2	26.7	..	.6	1475
Side	18.1	54.2	2.1	15.8	27.5	..	.7	1500
Mutton (cooked and canned).								
Leg, roast	..	50.9	2.1	24.3	21.5	..	.9	1410
Corned, canned	..	45.8	3.0	27.9	21.7	..	3.2	1495
Tongue, canned	..	47.6	3.1	23.7	22.8	..	3.6	1045
Pork (fresh).								
Chuck, ribs and shoulder.	18.1	51.1	2.3	16.8	29.5	..	.7	1605
Flank	18.0	59.0	1.9	17.9	21.1	..	.8	1265
Loin, chops	19.7	52.0	2.2	16.1	28.6	..	.8	1555
Ham	10.7	53.9	2.1	14.8	27.5	..	.6	1480
Shoulder	12.4	51.2	2.3	12.9	32.5	..	.6	1660
Side	11.5	34.4	3.2	8.8	52.5	..	.4	2440
Pork (pickled, salted and smoked).								
Bacon	7.7	18.8	4.8	9.6	64.0	..	3.3	2950
Ham	13.6	40.3	3.6	15.8	36.9	..	3.6	1905
Shoulder	18.2	45.0	3.8	15.4	30.9	..	5.0	1640
Salt, lean ends	11.2	19.9	5.1	8.1	63.7	..	4.3	2905
Salt, fat	..	7.9	5.4	1.8	81.9	..	2.9	3565
Pigs' feet, pickled	35.5	68.2	1.4	15.8	14.1	..	.7	920
Pork (cooked).								
Ribs, cooked	..	33.6	3.1	24.1	35.7	..	1.7	2020
Steak, cooked	..	33.2	3.3	19.3	43.1	..	1.1	2245
Sausage.								
Bologna	3.3	60.0	2.4	18.1	16.7	0.3	2.8	1085
Frankfort	..	57.2	2.3	19.0	17.7	1.1	2.6	1160
Pork	..	39.8	3.1	12.6	42.0	1.1	1.7	2080
Poultry and game (fresh).								
Chicken, broilers	41.6	74.8	1.0	20.9	2.4	..	.8	520
Fowl	25.9	63.7	1.6	18.7	15.5	..	.8	1040
Goose	17.6	46.7	2.5	15.8	34.4	..	.6	1800
Turkey	22.7	55.5	1.9	20.5	21.8	..	.8	853

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

KIND OF FOOD MATERIAL.	Inedible Refuse of Purchased Material.	EDIBLE PORTION.						
		Water.	Unavailable Nutrients.	AVAILABLE NUTRIENTS.				
				Proteid.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
ANIMAL FOODS.	%	%	%	%	%	%	%	Calories.
Poultry and game (cooked and canned).								
Capon	10.4	59.9	1.7	26.2	10.9	..	1.0	995
Turkey, roast	..	67.5	1.3	17.1	10.9	.8	2.4	855
Plover, roast, canned	..	57.7	1.7	21.7	9.7	1.6	7.6	985
Quail, canned	..	66.9	1.6	21.1	7.6	1.1	1.7	780
Fish (fresh).								
Bass, black, whole	54.8	76.7	1.0	20.0	1.6	..	.9	470
Bluefish	48.6	78.5	1.0	18.8	1.1	..	1.0	420
Codfish, dressed	29.9	58.5	.5	10.8	.2	..	.6	225
Cod steaks	9.2	79.7	.9	18.1	.5	..	.9	385
Flounder, whole	61.5	84.2	.7	13.8	.6	..	1.0	300
Haddock	51.0	81.7	.8	16.7	.3	..	.9	345
Halibut steak	17.7	75.4	1.1	18.0	4.9	..	.8	570
Lake trout	48.5	70.8	1.3	17.3	9.8	..	.9	765
Mackerel	44.7	73.4	1.3	18.1	6.7	..	.9	650
Weakfish	51.9	79.0	.9	17.3	2.3	..	.9	445
Whitefish, whole	53.5	69.8	1.4	22.2	6.2	..	1.2	710
Shell fish (fresh).								
Long clams, in shell	41.9	85.8	1.0	8.3	.9	2.0	2.0	240
Round clams, in shell	67.5	86.2	.9	6.3	.4	4.2	2.0	215
Oysters, in shell	81.4	86.9	.8	6.0	1.1	3.7	1.5	235
Oysters, solids	..	88.3	.6	5.8	1.2	3.3	.8	225
Clams, round, solids	..	80.8	1.0	10.3	1.0	5.2	1.7	340
Crabs, hard shells	52.4	77.1	1.4	16.1	1.9	1.2	2.3	425
Lobster	61.7	79.2	1.1	15.9	1.7	.4	1.7	400
Fish (preserved and canned).								
Cod, salt	24.9	53.5	6.8	20.9	.3	..	18.5	430
Cod, salt, boneless	1.6	55.0	5.5	24.9	.3	..	14.3	510
Halibut, smoked	7.0	49.4	5.0	20.1	14.3	..	11.3	1015
Herring, smoked	44.4	34.6	5.2	35.8	15.0	..	9.9	1360
Mackeral, salt, dressed	19.7	43.4	5.0	16.8	25.1	..	9.7	1415
Salmon, canned	14.2	63.5	1.9	21.1	11.5	..	2.0	915
Sardines, canned	5.0	52.3	3.1	22.3	18.7	..	4.2	1250
Lobster, canned	..	77.8	1.3	17.6	1.0	.4	1.9	400
Clams, canned	..	82.9	1.0	10.2	.8	3.0	2.1	290
Oysters, canned	..	83.4	.8	8.5	2.3	3.9	1.1	340

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

KIND OF FOOD MATERIAL.	Inedible Refuse of Purchased Material.	EDIBLE PORTION.						
		Water.	Unavailable Nutrients.	AVAILABLE NUTRIENTS.				
				Proteid.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
ANIMAL FOODS.	%	%	%	%	%	%	%	Calories.
Eggs.								
Eggs, uncooked	11.2	73.7	1.1	13.0	10.0	..	.8	695
Eggs, boiled	11.2	73.2	1.2	12.8	11.4	..	.6	755
Dairy products, etc.								
Whole milk	..	87.0	.5	3.2	3.8	5.0	.5	310
Skim milk	..	90.5	.3	3.3	.3	5.1	.5	170
Condensed milk, sweetened	..	26.9	1.2	8.5	7.9	54.1	1.4	1460
Cream	..	74.0	1.1	2.4	17.6	4.5	.4	860
Cheese	..	34.2	3.4	25.1	32.0	2.4	2.9	1885
Butter	..	11.0	4.9	1.0	80.8	..	2.3	3410
Oleomargarine, etc	..	9.5	5.7	1.2	78.9	..	4.7	3335
Lard, cottolene, etc	..	..	5.0	..	95.0	..	..	3985
ANIMAL FOOD.								
Miscellaneous.								
Gelatin	..	13.6	3.2	88.7	.1	..	1.6	2125
Calf's-foot jelly	..	77.6	.3	4.2	..	17.4	.5	410
VEGETABLE FOODS.								
Cereals, etc.								
Barley, pearled	..	11.5	4.0	6.6	1.0	76.1	.8	1630
Buckwheat flour	..	13.6	3.5	5.2	1.1	75.9	.7	1600
Buckwheat, self-raising	..	11.6	4.9	6.7	1.1	71.5	4.2	1545
Corn (maize) flour	..	12.6	3.6	5.8	1.2	76.3	.5	1625
Corn (maize) meal	..	12.5	4.0	7.5	1.7	73.5	.8	1625
Corn (maize) preparations:								
Cerealine	..	10.3	4.2	7.8	1.0	76.3	.4	1655
Hominy	..	11.8	3.8	6.8	.5	76.9	.2	1625
Hominy, cooked	..	79.3	.9	1.8	.2	17.4	.4	375
Oatmeal and rolled oats	..	7.8	5.6	13.4	6.6	65.2	1.4	1795
Oatmeal, boiled	..	84.5	.9	2.3	.5	11.3	.5	285
Rice	..	12.3	3.7	6.5	.3	76.9	.3	1610
Rice, boiled	..	72.5	1.1	2.3	.1	23.8	.2	505
Rye flour	..	12.9	3.6	5.3	.8	76.9	.5	1610
Entire wheat flour	..	11.4	4.5	10.7	1.7	70.9	.8	1645
Gluten flour	..	12.0	4.6	11.0	1.6	70.1	.7	1630
Graham flour	..	11.3	4.7	10.3	2.0	70.4	1.3	1640
Wheat flour, patent process:								
Low grade	..	12.0	4.5	10.9	1.7	70.2	.7	1635
Baker's grade	..	11.9	4.2	10.3	1.4	71.7	.5	1640

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

KIND OF FOOD MATERIAL.	Inedible Refuse of Purchased Material.	EDIBLE PORTION.						
		Water.	Unavailable Nutrients.	AVAILABLE NUTRIENTS.				
				Proteid.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
VEGETABLE FOODS.	%	%	%	%	%	%	%	Calories.
Cereals, etc.								
Family and straight grade	..	12.8	4.0	8.3	1.0	73.5	.4	1615
High grade	..	12.4	4.0	8.7	.9	73.6	.4	1620
Wheat preparations:								
Breakfast foods	..	9.6	4.5	9.3	1.6	74.0	1.0	1670
Macaroni	..	10.3	4.5	10.4	.8	73.0	1.0	1640
Macaroni, cooked	..	78.4	1.3	2.3	1.4	15.6	1.0	405
Spaghetti	..	10.6	4.0	9.4	.4	75.1	.5	1640
Noodles	..	10.7	4.2	9.1	.9	74.3	.8	1640
Bread:								
Brown	..	43.6	2.8	4.2	1.6	46.2	1.6	1035
Corn (johnnycake)	..	38.9	3.5	6.5	4.2	45.2	1.7	1170
Rye	..	35.7	3.4	7.3	.5	52.0	1.1	1160
Graham	..	35.7	3.4	6.9	1.6	51.3	1.1	1185
Whole wheat	..	38.4	3.2	7.5	.8	49.1	1.0	1125
White wheat	..	35.3	3.3	7.1	1.2	52.3	.8	1195
Biscuit, soda*	..	22.9	4.7	7.2	12.3	51.8	1.1	1655
Rolls	..	29.2	3.6	6.9	3.7	55.8	.8	1360
Toasted bread	..	24.0	4.1	8.9	1.4	60.3	1.3	1390
Crackers:								
Boston (split)	..	7.5	5.0	8.5	7.7	69.9	1.4	1830
Milk, cream	..	6.8	5.0	7.5	10.9	68.5	1.3	1920
Graham	..	5.4	4.8	7.7	8.5	72.5	1.1	1900
Oyster	..	4.8	5.4	8.8	9.5	69.3	2.2	1905
Soda	..	5.9	4.9	7.6	8.2	71.8	1.6	1870
Water	..	6.8	5.0	8.3	7.9	70.6	1.4	1850
Cakes, cookies, etc.:								
Bakers' cake	..	31.4	3.3	4.8	4.1	55.8	.6	1335
Coffee cake	..	21.3	3.8	5.5	6.8	61.9	.7	1580
Gingerbread	..	18.8	4.3	4.5	8.1	62.1	2.2	1620
Sponge cake	..	15.3	4.4	4.8	9.6	64.5	1.4	1735
Drop cake	..	16.6	4.5	5.9	13.2	59.2	.6	1805
Molasses cookies	..	6.2	4.7	5.6	7.8	74.0	1.7	1855
Sugar cookies	..	8.3	4.5	5.4	9.2	71.6	1.0	1865
Ginger snaps	..	6.3	4.7	5.0	7.7	74.3	2.0	1845
Wafers	..	6.6	4.8	6.7	7.7	73.0	1.2	1855
Doughnuts	..	18.3	4.8	5.2	18.9	52.1	.7	1895
Pie, pudding, etc.:								
Pie, apple	..	42.5	3.1	2.4	8.8	41.8	1.4	1215
Pie, custard	..	62.4	2.2	3.2	5.7	25.7	.8	795
Pie, squash	..	64.2	2.4	3.4	7.6	21.4	1.0	800

* Made from wheat flour, raised with baking powder.

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
				Available Nutrients.				
		Water.	Unavailable Nutrients.	Proteid.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
Vegetable Foods.	%	%	%	%	%	%	%	Calories.
Cereals, etc.								
Pie, pudding, etc.:								
Pudding, Indian meal	..	60.7	2.5	4.5	4.3	26.9	1.1	785
Pudding, rice custard.	..	59.4	2.1	3.2	4.1	30.7	.5	825
Pudding, tapioca.....	..	64.5	1.0	2.8	2.9	28.2	.6	715
Sugars, starches, etc.								
Sugar, granulated........	..	..	..	..	..	100.0	..	1790
Sugar, pulverized........	..	..	..	..	..	100.0	..	1790
Sugar, brown............	..	..	..	..	..	95.0	..	1700
Sugar, maple............	..	..	..	..	..	82.8	..	1485
Molasses...............	..	..	..	..	..	70.0	..	1255
Maple syrup............	..	..	..	..	..	71.0	..	1270
Cornstarch	..	..	..	..	..	90.0	..	1715
Tapioca................	..	11.4	.1	.3	.1	88.0	.1	1685
Sago..................	..	12.2	1.4	7.7	.4	78.1	.2	1665
Vegetables.								
Asparagus, fresh.........	..	94.0	.7	1.3	.2	3.3	.5	95
Asparagus, cooked.......	..	91.6	1.0	1.7	3.0	2.1	.6	195
Beans, Lima, green......	55.0	68.5	2.7	5.3	.6	21.6	1.3	525
Beans, Lima, dried......	..	10.4	6.7	12.8	1.4	65.6	3.1	1565
Beans, string, fresh......	7.0	89.2	1.0	1.7	.3	7.2	.6	180
Beans, string, cooked *...	..	95.3	.5	.6	1.0	1.9	.7	90
Beans, white, dried......	..	12.6	7.5	15.8	1.6	59.9	2.6	1530
Beans, baked............	..	68.9	2.8	4.8	2.3	19.6	1.6	565
Beets, fresh.............	20.0	87.5	1.0	1.2	.1	9.4	.8	205
Beets, cooked*..........	..	88.6	1.2	1.7	.1	7.2	1.2	170
Beet "greens," cooked*..	..	89.5	1.2	1.7	3.1	3.2	1.3	220
Cabbage................	15.0	91.5	.7	1.2	.3	5.5	.8	140
Carrots, fresh...........	20.0	88.2	1.0	.7	.4	8.9	.8	200
Carrots, evaporated......	..	3.5	6.9	5.8	3.2	76.9	3.7	1700
Cauliflower.............	..	92.3	.7	1.3	.5	4.7	.5	135
Celery..................	20.0	94.5	.6	.8	.1	3.2	.8	80
Sweet corn, green........	61.0	75.4	1.8	2.3	1.0	19.0	.5	445
Cucumbers..............	15.0	95.4	.4	.6	.2	3.0	.4	75
Egg plant...............	..	92.9	.6	.9	.3	4.9	.4	120
Lettuce.................	15.0	94.7	.5	.9	.3	2.9	.7	85
Onions, fresh...........	10.0	87.6	.8	1.2	.3	9.6	.5	215
Onions, cooked*.........	..	91.2	.8	.9	1.6	4.8	.7	175
Parsnips................	20.0	83.0	1.2	1.2	.5	13.0	1.1	290
Peas, dried..............	..	9.5	7.6	17.3	.9	62.5	2.2	1508

* With butter, etc., added.

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

KIND OF FOOD MATERIAL.	Inedible Refuse of Purchased Material.	EDIBLE PORTION.						
				AVAILABLE NUTRIENTS.				
		Water.	Unavailable Nutrients.	Proteid.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
VEGETABLE FOODS.	%	%	%	%	%	%	%	Calories.
Vegetables.								
Peas, green	45.0	74.6	2.2	5.2	.5	16.7	.8	430
Peas, green, cooked*	..	73.8	2.5	5.1	3.1	14.4	1.1	490
Potatoes	20.0	78.3	1.4	1.7	.1	17.7	.8	370
Potatoes, cooked, boiled	..	75.5	1.7	1.9	.1	20.0	.8	415
Potatoes, mashed and creamed	..	75.1	2.0	2.0	2.7	17.1	1.1	475
Pumpkins	50.0	93.1	.6	.7	.1	5.0	.5	110
Radishes	30.0	91.8	.7	1.0	.1	5.6	.8	130
Rhubarb	40.0	94.4	.6	.4	.6	3.5	.5	100
Squash	50.0	88.3	.9	1.1	.5	8.6	.6	205
Spinach, fresh	..	92.3	1.0	1.6	.3	3.2	1.6	100
Spinach, cooked*	..	89.8	1.1	1.6	3.7	2.7	1.1	235
Sweet potatoes, fresh	20.0	69.0	2.1	1.3	.6	26.2	.8	545
Sweet potatoes, cooked*	..	51.9	3.0	2.2	1.9	40.3	.7	885
Tomatoes	..	94.3	.4	.7	.4	3.8	.4	100
Turnips	30.0	89.6	.8	1.0	.2	7.8	.6	175
Vegetables (canned).								
Asparagus	..	94.4	.6	1.2	.1	2.8	.9	80
Beans, baked	..	68.9	2.7	4.8	2.3	19.7	1.6	555
Beans, string	..	93.7	.7	.8	.1	3.7	1.0	90
Beans, Lima	..	79.5	1.7	3.0	.3	14.3	1.2	335
Sweet corn	..	76.1	1.7	2.1	1.1	18.3	.7	430
Peas, green	..	85.3	1.4	2.7	.2	9.6	.8	235
Succotash	..	75.9	1.8	2.7	.9	18.0	.7	425
Tomatoes	..	94.0	.5	.9	.2	3.9	.5	100
Fruits, etc. (fresh).								
Apples	25.0	84.6	1.6	.3	.5	12.8	.2	260
Apricots	6.0	85.0	1.5	.9	..	12.2	.4	240
Bananas	35.0	75.3	2.7	1.0	.5	19.9	.6	400
Blackberries	..	86.3	1.5	1.0	.9	9.9	.4	235
Cherries	5.0	80.9	2.0	.8	.7	15.1	.5	320
Cranberries	..	88.9	1.2	.3	.5	8.9	.2	190
Currants	..	85.0	1.7	1.2	..	11.6	.5	230
Figs	..	79.1	2.2	1.2	..	17.0	.5	330
Grapes	25.0	77.4	2.4	1.1	1.4	17.3	.4	390
Huckleberries	..	81.9	2.0	.5	.5	14.9	.2	300
Lemons	30.0	89.3	1.2	.8	.6	7.7	.4	180
Muskmelons	50.0	89.5	1.1	.5	..	8.4	.5	160
Oranges	27.0	86.9	1.4	.6	.2	10.5	.4	210

* With butter, etc., added.

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

KIND OF FOOD MATERIAL.	Inedible Refuse of Purchased Material.	EDIBLE PORTION.						
				AVAILABLE NUTRIENTS.				
		Water.	Unavailable Nutrients.	Proteid.	Fat.	Carbohydrate.	Ash.	Fuel Value per lb. = 453.6 Grams.
VEGETABLE FOODS.	%	%	%	%	%	%	%	Calories.
Fruits, etc. (fresh).								
Pears	10.0	84.4	1.7	.5	.4	12.7	.3	255
Plums	5.0	78.4	2.2	.8	..	18.2	.4	345
Prunes	6.0	79.6	2.1	.7	..	17.1	.5	325
Raspberries, black	..	84.1	1.7	1.4	.9	11.4	.5	270
Strawberries	5.0	90.4	1.0	.8	.5	6.8	.5	160
Watermelons	60.0	92.4	.9	.3	.2	6.0	.2	125
Fruits, etc. (dried).								
Apples	..	28.1	7.5	1.3	2.0	59.6	1.5	1190
Apricots	..	29.4	7.7	3.7	.9	56.5	1.8	1130
Citron	..	19.0	8.3	.4	1.3	70.3	.7	1340
Currants	..	17.2	8.6	1.9	1.5	67.0	3.8	1315
Dates	10.0	15.4	8.8	1.6	2.5	70.7	1.0	1415
Figs	..	18.8	8.7	3.4	.3	67.0	1.8	1290
Raisins	10.0	14.6	9.1	2.0	3.0	68.7	2.6	1410
Prunes	15.0	22.3	8.3	1.6	..	66.1	1.7	1230
Fruits, etc. (canned).								
Apricots	..	81.4	1.9	.7	..	15.7	.3	295
Blackberries	..	40.0	6.1	.6	1.9	50.9	.5	1015
Blueberries	..	85.6	1.6	.5	.5	11.5	.3	240
Cherries	..	77.2	2.3	.9	.1	19.1	.4	365
Crab-apples	..	42.4	5.7	.3	2.2	49.0	.4	985
Peaches	..	88.1	1.3	.5	.1	9.8	.2	190
Pears	..	81.1	1.9	.3	.3	16.2	.2	310
Strawberries (stewed)	..	74.8	2.6	.5	..	21.7	.4	400
Nuts.								
Almonds	45.0	4.8	10.9	17.8	49.4	15.6	1.5	2685
Butternuts	86.0	4.4	11.4	23.7	55.1	3.2	2.2	2805
Chestnuts (fresh)	16.0	45.0	5.9	5.3	4.9	37.9	1.0	990
Cocoanuts	49.0	14.1	9.2	4.8	45.5	25.1	1.3	2460
Filberts	52.0	3.7	10.7	13.3	58.8	11.7	1.8	2930
Hickorynuts	62.0	3.7	10.6	13.1	60.7	10.3	1.6	2980
Peanuts	25.0	9.2	10.7	21.9	34.7	22.0	1.5	2255

For greater detail see The Chemical Composition of American Food Materials, by Atwater and Bryant, Bulletin 28 (Revised), U. S. Dept. of Agriculture, Washington, 1902.

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