nation of carbon dioxide and water, and the heightened consumption of oxygen bear witness to the source of the energy set free. A few figures from actual experiments will best illustrate this statement. Thus the following table compiled from the determinations of Atwater and Benedict on healthy men indicate the increased metabolic activity incidental to work as shown by the increased output of carbon dioxide. Some details of the changes brought about will be considered later, in particular the nature of the body constituent burned up.

TABLE M.—CARBON DIOXIDE ELIMINATED BY LUNGS AND SKIN DURING REST AND WORK.

Kind of experiment.	Days covered by experiments.	Total amount in twenty-four hours. Grams.	Rate Per Hour.				Average for twenty-four hours. Grams.	Proportion of Total for Twenty-Four Hours.			
			Day Periods.		Night Periods.			Day Periods.		Night Periods.	
			7 A.M. to 1 P.M. Grams.	1 P.M. to 7 P.M. Grams.	7 P.M. to 1 A.M. Grams.	1 A.M. to 7 A.M. Grams.		7 A.M. to 1 P.M. Per cent.	1 P.M. to 7 P.M. Per cent.	7 P.M. to 1 A.M. Per cent.	1 A.M. to 7 A.M. Per cent.
Rest	45	794	37.8	37.2	35.0	22.4	33.1	38.6	28.1	26.4	16.9
Work	20	1,253	75.5	76.6	34.1	22.6	52.3	36.2	35.7	16.3	10.8

The elimination of carbon dioxide during the working hours is twice as large as during the corresponding hours of the rest days. In these experiments the heat equivalent of the external muscular work done was only 6.4 per cent. of the total energy given off from the body in different ways.

The following data, taken from experiments on man by Katzenstein, show the intensity of the metabolic changes which work brings about, as expressed in the consumption of oxygen per minute in contrast with the conditions prevailing during rest: During rest, 263 c.c.; walking on level, 763 c.c.; walking uphill, 1,253 c.c.

Rubner has calculated the total metabolism of a large number of individuals on the basis of an average body weight, and expressed in heat units (kilocalories), thus:

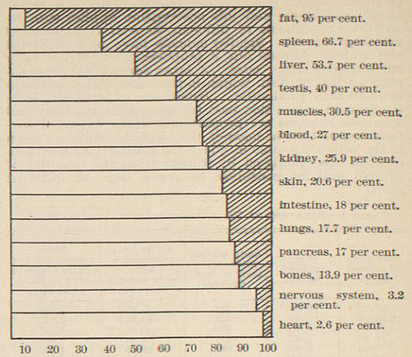
TABLE N.

During rest	2,303 cal.	=	32.9 cal. per kilo.		
Slight bodily work (physicians, etc.)	2,442 "	=	34.9 " "	=	6% increase.
Medium bodily work (soldiers, etc)	2,868 "	=	41.0 " "	=	24% "
Severe work (machinists, etc.)	3,362 "	=	48.0 " "	=	45% "
Exhausting work (miners, etc.)	4,790 "	=	68.4 " "	=	108% "

Finally, the important influence of training must be noted in this connection. It has repeatedly been shown that the trained individual works more economically, *i.e.*, utilizes less potential energy in accomplishing the same muscular task. No specific effects attributable to mental activity or to sleep have yet been detected. The slightly diminished metabolism during sleep is usually ascribed to the absence of all muscular effort.

In considering the influence which the various constituents of the diet exert upon metabolism, it may be well to take up first the changes which go on in the absence of food, *i.e.*, in *starvation* or inanition. Certain species are adapted by nature to undergo prolonged hunger without serious harm. This is true of hibernating animals, such as the marmot and the bear, in which the vital processes are at an ebb during certain portions of the year. In most animals, however, katabolism continues uninterruptedly during starvation. The body consumes its own tissues, and the extent of the changes will depend somewhat upon the previous nutritive condition of the individual. The store of fat is the first to be called on, and the relative participation of the various organs and tissues is shown graphically in the chart constructed from Voit's analyses of starved animals.

TABLE O.—GRAPHIC REPRESENTATION OF THE PERCENTAGE OF TISSUES LOST DURING STARVATION. THE SHADED AREAS REPRESENT LOSS, THE UNSHADED AREAS RESIDUE AT DEATH. (From Waller.)



An inspection of the diagram above brings to light the significant fact that those organs, viz., the heart and central nervous system, which serve the body in most important capacities are not drawn upon until the very end. Thus they work at the expense of the other tissues. During starvation urea continues to be excreted in the urine, the quantity being rather large for a day or two and then reaching a daily level which may remain fairly constant for some time. This level, it may reasonably be assumed, represents the extent of proteid katabolism necessary for the continuance of the bodily functions. Where there is an abundance of body fat, the nitrogen output may remain at a low figure for some time. The sudden rise in urea excretion before death intervenes has been interpreted to indicate that the fat has largely been used up and that tissue proteids are thenceforth called upon to yield the entire energy liberated. Some of the experiments on fasting men who were previously well nourished indicate a low nitrogen output, as low as 3.2 gm. per day being obtained by Luciani at the end of Succi's thirty days' fast. In other cases a somewhat larger output has been found. Thus in careful experiments by Zuntz, I. Munk, and others in Berlin on the "professional faster" Cetti and on Breithaupt, the data following were obtained from examination of the urine. The nitrogen has been calculated to proteid (N × 6.25).

TABLE P.

Day.	Cetti.		Breithaupt.	
	Nitrogen output. Grams.	Equivalent in Proteids. Grams.	Nitrogen output. Grams.	Equivalent in proteid. Grams.
Before fasting	13.49	84.9	13.02	82.0
First hunger day	13.545	85.3	10.01	63.1
Second hunger day	12.586	79.3	9.92	62.5
Third hunger day	13.121	82.7	13.29	83.7
Fourth hunger day	12.393	78.1	12.78	80.5
Fifth hunger day	10.695	67.4	10.95	68.9
Sixth hunger day	10.100	63.6	9.98	62.2
Seventh hunger day	10.855	68.6		
Eighth hunger day	8.903	56.1		
Ninth hunger day	10.833	68.2		
Tenth hunger day	9.467	50.7		
First eating day	13.35	84.1	11.88	74.7

Of the total loss of body weight during inanition, about two-thirds may be ascribed to loss of water, and the remaining one-third to body proteid and fat, the relative proportion of the latter being determined by the previous nutritive condition. It is therefore obvious that complete inanition is more far-reaching in its effects and less readily endured than starvation in which water is consumed. During hunger the fæces which continue to be passed from the intestine have their origin in materials poured into the alimentary canal. In appearance the "hunger fæces" resemble those following a diet rich in meat; and the thought is at once suggested that the fæces ordinarily discharged after an easily digestible diet consist, principally, of secretory products from the alimentary tract, and are not to be considered as the undigested residue of the food to any great extent. In the experiments on Cetti and Breithaupt quoted above, the average daily quantity of dry substance in the fæces was 3.8 and 2 gm. respectively, having a nitrogen content of from five to eight per cent. Normal fæces ordinarily contain from three to four per cent. of nitrogen.

To the physician the study of metabolism in hunger is of interest in connection with the observations made in various conditions of deficient nutrition, or malnutrition. In many of these cases the proteid metabolism may fall to a very low limit, especially where the contributory causes are gradual in their onset and where, as in paralysis, there is little bodily movement to call upon the store of energy.

It will be impossible, within the brief limits of this article, to discuss in detail the influences which the various factors of the diet exert on metabolism, and on proteid metabolism in particular. The dogmatic statements which may be made must be accepted with some reserve, since a vast number of modifying conditions must be taken into consideration in each case. The tendency toward the establishment of *nitrogenous equilibrium* has already been referred to. Briefly it may be expressed as follows: On a diet sufficient to cover the calorimetric needs of the body, the extent of nitrogenous (proteid) metabolism is determined within certain wide limits by the intake of nitrogenous food. For the lower limit about 0.5 gm. of proteid per kilogram of body weight may be accepted, a normal figure (Voit's) being 1.5 gm. per kilogram. These figures are exclusive of the losses through the fæces. The latter will vary somewhat with the nature of the diet, certain forms of vegetable proteid being utilized less readily than the proteids of meat. The differences are, however, merely due to differences in the digestibility and absorption of the two classes of materials, occasioned by the character of the vegetable foods with their cellulose structures. So far as is known at present, the pure vegetable proteids undergo changes in metabolism directly comparable with those ascertained for the proteids of animal origin.

In man nitrogenous equilibrium can be attained for a short time on a purely proteid (meat) diet. The large quantity of such food which is necessary is eaten and digested only with great difficulty. The process of "putting on flesh" in distinction from "laying on fat" is accordingly confined to a few general conditions of nutrition. These include the periods of growth and of convalescence after wasting disease or deficient nutrition. The determining factor in any case is the immediate nutritive state of the tissue cells; and thus in part is explained the hypertrophic growth of muscles incidental to increased activity. The condition of the cell rather than the character of the food material is perhaps the important element here. Undoubtedly variations occur with the species as with the individual in this respect; and Pflüger has pointed out cases in which the growth of the total cell substance may be assumed to be doubled after proteid feeding. A most peculiar fact is the marked increase in proteid metabolism and in total metabolism brought about by increasing the proteid of the diet. This is indicated in the following table constructed by Tigerstedt from the experimental data of Pettenkofer and Voit.

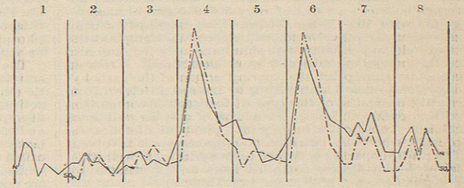
TABLE Q.—EFFECT OF PROTEID DIET ON METABOLISM.

Number of experiment.	Nitrogen Intake. Grams.	Nitrogen output. Grams.	Gain (+) or loss (−) of fat. Grams.	Total metabolism (heat production). Kilocalories.
1	0	5.61	− 98	1,064
2	17	20.37	− 61	1,106
3	34	36.69	− 43	1,360
4	51	51.00	− 24	1,552
5	61	59.74	− 36	1,893
6	68	69.50	+ 8	1,741
7	85	85.41	+ 4	2,181

The calculation of the total metabolism in units of heat produced in No. 7 gives results twice as large as those obtained during hunger (No. 1), while the proteid metabolism undergoes a manifold stimulation. Upon such facts depends the efficiency of some of the prevalent modes of treatment for obesity. The large proportion of proteid in the diets prescribed provokes a relatively large waste of tissue substance, especially when the total intake is comparatively small for the daily needs.

The sulphur and phosphorus of the proteids, oxidized in metabolism to sulphuric acid and phosphoric acid, are excreted as salts in the urine. Their elimination usually runs closely parallel to that of nitrogen, the quantity of sulphates taken in with the diet being very small. The determination of the sulphates of the urine affords a valuable means of controlling experiments on proteid metabolism, especially where non-proteid nitrogenous substances (such as amido-acids) are ingested. The diagram presented below shows the relative fluctuations in the average rates of excretion of N and SO_3 in the experiments of Sherman and Hawk on men living on a fixed diet. The estimations were made at intervals during the day, and the values on the left represent percentages of an assumed standard rate of excretion for each of the constituents. The parallel vertical lines separate the successive days. On the fourth and sixth days large additional quantities of proteid were consumed. It will be seen that in general the excretion of sulphates ran quite parallel to that of nitrogen.

TABLE R.—EXCRETION OF N AND SO_3.



The phosphoric acid of the urine represents one of the end-products of the katabolism of nucleoproteids, and an increased elimination of it may be interpreted as evidence of nuclear waste in the body, if no nucleic acid compounds (such as occur abundantly in thymus, pancreas, etc.) or phosphorized proteids (pseudonucleins) like casein are ingested. Conditions may arise in which the exact parallelism between N and P excretion is abolished. Röhmann and his pupils have shown that these phosphorized proteids have a peculiar importance in nutrition, and that phosphorus in the form of inorganic phosphates cannot completely replace such organic com-

pounds of phosphorus as are represented by casein and vitellin.

We have seen that the body may soon reach nitrogen equilibrium after ingestion of considerable quantities of proteid. The study of the time within which the extra nitrogen is again eliminated has indicated that the proteid is quickly broken down in metabolism. A glance at the diagram of N and SO_3 excretion presented above verifies this. When lean beef sufficient to furnish about 64 gm. of extra proteid was taken with breakfast on the two days indicated, the nitrogen of the urine began to rise in the first three hours and reached a maximum between the sixth and ninth hours, after which it declined at first rapidly and then more slowly, reaching its normal after about thirty-six to thirty-nine hours. The nature and extent of the changes in the urine seem to have been about the same when the proteid was simply added to the diet as when it was substituted for an isodynamic amount of fat.

A consideration of the influence of the non-nitrogenous foodstuffs, the fats and carbohydrates, leads to conclusions quite different from those drawn for the proteids. It is evident that the non-nitrogenous foods cannot be fed alone for any length of time without bringing about effects comparable with those obtained during hunger. The chief interest regarding their behavior in metabolism therefore lies in the influence which they exert on nitrogenous or proteid katabolism. In general, it may be stated that the fats and carbohydrates, even when fed in large quantities, fail to increase metabolism in any such degree as does proteid feeding. On the contrary, the presence of non-nitrogenous constituents in the diet tends to diminish the amount of proteid required to bring the body into nitrogenous equilibrium. The fats and carbohydrates, and the so-called "carbon moiety" of the proteids, *i.e.*, the portion remaining after the deduction of sufficient carbon to unite with the nitrogen to form urea, may all be deposited in the organism in the form of fat or glycogen. Or, again, by being burned up they may protect the tissue fat from katabolism and in this case likewise bring about a diminished loss or resultant gain to the body. This is known as *proteid-sparing* action. The adipose tissue of the body may apparently act in a manner analogous to that of the fat of the diet. It is generally admitted that the proteid-sparing power of carbohydrate food is distinctly greater than that of the fats. Indeed a quantity of proteid which fails to produce nitrogen equilibrium may do so when carbohydrate is added to the diet. The same is true to a lesser degree in the case of fats. Thus a dog which required 1 kgm. of meat to reach N equilibrium was observed to show a similar nitrogen balance on a diet of only 500–600 gm. of meat together with 100–150 gm. of fat. The extent of fat utilization, on the other hand, will depend on the quantities of proteid and carbohydrate simultaneously fed, and also on the amount of muscular work performed. From an economic standpoint the sparing action of the carbohydrates on proteid katabolism is of interest in view of the relative cheapness of this type of foodstuff in comparison with proteids and fats. Problems of cost as well as of efficiency must enter largely into practical dietetics, especially where the nutrition of large masses is involved. The proteid-sparing action of carbohydrates is well illustrated by the figures compiled from an experiment by I. Munk on a dog of 28 kgm. (see Table S).

No consideration of the influence of the various dietary constituents would be complete without reference to a number of accessory substances either commonly taken with the food or closely related to the foodstuffs proper. Thus the albuminoid *gelatin* enters into ordinary diet to a considerable extent. Although it contains nitrogen in practically the same proportions as this element exists in the simple proteids, gelatin cannot completely replace the latter. Experiments on animals have shown that when gelatin is fed exclusively, tissue proteids are always consumed in excess of the gelatin introduced and sooner or later serious symptoms intervene. For example, a 50 kgm. dog living on 200 gm. of gelatin, 250 gm.

Table S.—Effect of Carbohydrates on Proteid Metabolism.

Food.		Flesh.	
Meat. Grams.	Carbohydrates. Grams.	Metabolized. Grams.	Gain (+) or loss (−). Grams.
200	250	263	− 63
200	300	223	− 23
200	500	201	− 1
200	500	172	+ 28
200	500	132	+ 68
200	500	168	+ 32
200	500	122	+ 78

of starch, 100 gm. of fat, and 12 gm. of beef extract per diem died in thirty days as a result of continued proteid katabolism (I. Munk). Ingested with proteid and other foodstuffs, however, gelatin exerts a noticeable proteid- and fat-sparing action and thus behaves like a non-nitrogenous food. It has been found possible to replace as much as five-sixths of the proteid of the diet with gelatin without unfavorable outcome.

In view of the peptonization which proteids undergo in the digestive processes it has been asked whether the various hydration products, *albumoses* and *peptones* in particular, can replace ordinary proteids. A practical aspect of the problem is seen in the present widespread use of predigested or partially digested foods. From the data available the statement seems justifiable that some of these may replace proteid without disturbance of the nitrogenous equilibrium of the individual. Recent investigation has indicated that distinct differences occur in various digestive products, and as yet no experiments in this direction have been sufficiently prolonged to permit any far-reaching statements. Whether the non-proteid nitrogenous compounds (such as *asparagin* and *amido-acids*) can undergo a synthesis to proteid—as Loewi has recently suggested (1902)—remains to be seen. *Fatty acids* have been observed to exert the same proteid-sparing action as comparable quantities of fat. The physiological action of *alcohol* has formed the subject of much controversy. It seems certain, however, that moderate quantities are almost completely oxidized, and in non-toxic doses probably may exert a slight proteid-sparing action. The function of the *inorganic salts* of the diet is apparently exerted more in directing the metabolism of the body than in any immediate participation in the exchange of materials. Their importance is fully demonstrated by the serious effects which follow the removal of even single elements from the diet. At certain periods Ca, Fe, etc., enter into synthetic processes. Large quantities of common tissue constituents, such as chlorides and phosphates, tend in general to exert an increased action on the metabolism of proteids.

The general features of metabolism during muscular activity have already been reviewed. There can be little question that the muscles themselves are the seat of active chemical change. It is sufficient to point to the disappearance of glycogen from the contracting muscle and the appearance of products like carbon dioxide and lactic acid. The lymph bathing the muscle cells is called upon to furnish oxygen and organic compounds, while it carries away the products of katabolism. We are now in a position to consider what are the sources of the energy expended. Are the nitrogenous or non-nitrogenous constituents drawn upon in muscular work? The older view of Liebig that the muscles work entirely at the expense of their proteid constituents was conclusively overthrown by the investigations of Voit and his successors. The output of carbon dioxide and water is promptly increased by muscular activity to an extent directly proportional to the work done. With reference to nitrogenous metabolism no such effect can be noted. Under satisfactory conditions of diet the elimination of urea is scarcely, if any, greater during work than with the same intake of proteid during rest. This indicates clearly that the non-nitrogenous compounds are the chief

sources of the energy expended by the muscles. Many statistical facts are in harmony with this. Thus the diet of the laboring classes compared with that of less active persons does not contain an excess of proteid sufficient to account for more than a small fraction of the extra work done and heat produced, as will be seen in the commonly accepted standards below.

Table T.—Comparison of Dietary Standards.

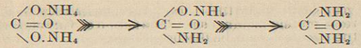
Subject.	Proteids. Grams.	Fats. Grams.	Carbohydrates. Grams.	Potential energy. Kilocal.
Man at moderate work (Voit)	118	56	500	3,055
Man at moderate work (Atwater)	125	....	....	3,500
Man at hard work (Voit)	145	100	450	3,370
Man at hard work (Atwater)	150	....	....	4,500

Actual metabolism experiments are in accord with what the statistical inquiry would lead us to expect. On an abundant mixed diet no marked increase in proteid katabolism attends periods of muscular work. When, however, the diet is too scanty to furnish the potential energy required, body proteid may be called upon to furnish the deficiency; and under these circumstances the nitrogen output in the urine is observed to be increased. The same phenomenon is observed after prolonged or severe exertion, although the extra nitrogen output may not occur until the day following the exercise. This suggests (as experience in training athletes shows) that the increased cellular activity of the muscles calls forth metabolic changes in the contractile tissue independently of the transformation of energy incidental to the work done. Pflüger has lately attempted to refer the source of muscular energy to proteid substances, since he succeeded in keeping a dog for weeks upon a diet of very lean meat and causing him to do a very large amount of muscular work during this period. Experiments of this sort merely show that in the absence of non-nitrogenous food the body can utilize proteid in liberating energy through the muscles. This is the less remarkable since recent investigation has made probable the existence of large carbohydrate groups in many of the proteids. As Schaefer has said in this connection: "The most probable view appears to be that the muscle, like other cells, although it can only build up the bioplasm out of proteid, is nevertheless able to produce muscular energy by the oxidation of any or all the organic foodstuffs, and that this process is attended only by such small disintegration and loss of the proteid material of the bioplasm as is necessarily attendant upon its functional activity—a loss which is comparable to the wear and tear of the working parts of the machine as distinct from its consumption of fuel."

Of other influences which may bear upon metabolism nervous excitement or *mental activity* apparently brings about no noticeable change in the katabolism of proteid or the utilization of fat. In the higher animals which maintain an approximately constant body temperature, changes in the surrounding temperature do not modify proteid metabolism. With increased *cold* more fat is used up by the organism. The influences of *age* and *sex* are largely dependent upon variations in the size of the body which condition the inequalities in heat regulation already discussed. In old age metabolism is less intense and the nutritive requirements are consequently diminished. The few experimental data at hand indicate that during the period of menstruation the output of nitrogenous waste may be diminished. A similar sparing of proteid appears to occur during the period of gestation. Many *drugs* exert pronounced effects on metabolism either directly or indirectly through the physiological reactions (such as muscular excitability, or sleep) which they provoke. Coffee and tea, and some of the more widely used food preservatives (borax, formaldehyde, etc.) have no extensive effects in this respect, when used in very small quantities. In larger doses they tend to increase proteid metabolism. The action of various therapeutic agents cannot be discussed here.

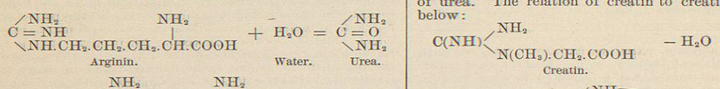
No account of metabolism in disease need be given in detail here, since the peculiar features are presented elsewhere under the descriptions of the various pathological states (see *Diabetes*, *Fever*, etc.). In *febrile diseases* it seems to be demonstrated that katabolism is stimulated and may be increased twenty-five per cent. beyond that which occurs in health. The extensive exchange of materials is usually associated with increased work of the heart and respiratory mechanism. To this may be added the results of the deficient nutrition which is common to the sick, and a specific effect of the toxic bacterial or protoplasmic products which may directly stimulate proteid metabolism. The destruction of the nitrogenous tissue compounds may proceed very rapidly in fever and lead to extreme emaciation, although total metabolism may not be more marked. In *diabetes* increased proteid katabolism usually occurs. It seems likely that this is a physiological consequence of the failure on the part of the organism to utilize carbohydrates; and in many of the milder types the loss of nitrogenous substance may be limited by an appropriate diet which will afford sufficient energy in place of the wasted sugar. The extensive proteid katabolism in the several forms of diabetes must, however, be attributed to toxic effects and to the perversions of metabolism peculiar to the disease. The effects of *hepatic disease* vary with the nature of the pathological condition. In icterus they are largely indirect, depending in part on the remote results of impaired digestion, while in cirrhosis and in acute atrophy of the liver we have to deal with inefficient hepatic cells. Thus it is that unusual end-products of proteid decomposition (such as leucin and tyrosin) make their appearance in the urine, and direct attention to the incompleteness of the chemical reactions in the cells which are ordinarily entrusted with important functions. In certain types of *leukæmia* there is evidence of disordered metabolism of the nuclein substances, giving evidence of itself in an increased output of uric acid and phosphates in the urine. In various forms of *anæmia* the peculiar perversion of metabolism consists in disturbances of internal respiration connected with the deficiency of blood pigment. Further disturbances of nutrition may be secondary. The metabolic phenomena in diseases of the *gastro-intestinal tract* are largely the outcome of malnutrition, the deficient work of the digestive mechanism perhaps being accompanied in some instances by an auto-intoxication. The whole subject of metabolism in disease deserves further study before more general conclusions can be drawn.

The history of the foodstuffs after their introduction into the organism is fragmentary and uncertain in many details. The formation of *urea*, $C{=}O{<}^{NH_2}_{NH_2}$, the most important nitrogenous end-product of the katabolism of simple proteids, can safely be assigned to the liver; although evidence is not wanting that small quantities may arise elsewhere, perhaps in the muscles. The nature of the intermediate steps still remains somewhat hypothetical. There is much in favor of the view that the proteid is first transformed to simple compounds like ammonia (NH_3) and carbon dioxide (CO_2), and that ammonium carbonate $(NH_4)_2CO_3$ may be the precursor of urea. It is not unlikely that the bulk of the proteid nitrogen leaves the various organs in the form of ammonium lactate, $C_2H_4(OH)COO.NH_4$, which is brought to the liver and there oxidized to carbonate. When the liver cells undergo degeneration, the amount of urea in the urine is diminished while the quantity of ammonium compounds is augmented. Furthermore, urea can be formed in the liver from ammonium carbonate, other ammonium salts, and even amido acids such as glycocoll, $CH_2(NH_2)COOH$. Drechsel assumed that the process took place with the formation of ammonium carbamate as an intermediate stage, as follows:



Ammonium carbonate. Ammonium carbamate. Urea.

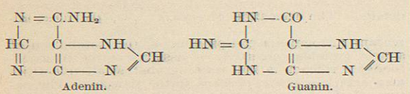
The possibility of a direct formation of urea from proteids is no longer excluded. By direct oxidation with permanganate in the presence of ammonia at 40° C. Hofmeister has succeeded in obtaining urea from various substances, both nitrogenous and non-nitrogenous. There is at present no experimental evidence to suggest that such oxidative syntheses actually occur in the body. Another source of urea may be found in arginin, $C_6H_{14}N_4O_2$, which is formed by the hydrolytic cleavage of proteids and by digestive enzymes. Arginin yields urea on decomposition as follows:



Arginin. Water. Urea. Ornithin.

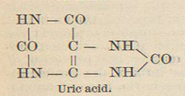
Gulewitsch has detected arginin in the spleen of the ox, and thus demonstrated that it may occur in the body. In view of all these facts, it is quite possible that urea may arise in a number of ways in metabolism and include one or more of the processes outlined. Other theories have been advanced in the past; but none of them has anything more decisive in its favor.

Of the purin derivatives (alloxuric bodies, xanthin bases) excreted in the urine, *uric acid* is the most important. In birds and reptiles it forms the chief nitrogenous end-product of metabolism, and results from synthetic processes taking place in the liver. In man and other mammals the origin of the uric acid is quite different. Here it represents one of the metabolic products of the nucleic acids. The latter are present in the diet in variable quantities and occur in nature in the so-called nucleoproteids (nucleates) which are salts of proteids with nucleic acid. On decomposition the nucleic acids yield one or more of the purin derivatives, usually adenin or guanin, which undergo oxidation in the body. Uric acid is an intermediate stage in the complete decomposition; when introduced as such into the body it is largely burned up. In some animals a further stage in the oxidation process, viz., allantoïn, is found in the urine after ingestion of uric acid or of nucleates. The relationship between these compounds is indicated by their structural formulæ:

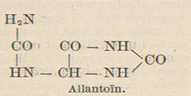


Adenin.

Guanin.



Uric acid.

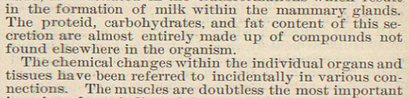


Allantoïn.

Experiments by the writer and others make it probable that the liver is the seat of the oxidations referred to. There is no evidence that the spleen is involved, as has been assumed. While the possibility of a synthetic formation of uric acid has not been absolutely excluded, it cannot play any important rôle under ordinary conditions. In the absence of purin compounds in the diet, the uric acid output in man does not ordinarily exceed 300 mgm. per day. Uric acid bears no direct relation to urea in metabolism, although the latter may be formed from it.

Hippuric acid (benzoyl-glycocoll) is a synthetic product formed through the agency of the kidney cells. The benzoic acid radical is introduced into the body with the diet, while glycocoll ($CH_2[NH_2]COOH$) is without doubt one of the intermediary products of proteid katabolism. It can be obtained directly from most proteids by hydrolytic cleavage.

Creatinin in the urine represents, for the most part, ingested creatinin, or creatin which is largely changed into creatinin in the body. The fact that neither of these compounds undergoes metabolism with production of urea or anything else accords with the general belief that these substances cannot build up proteids and presumably do not form an intermediate step in the formation of urea. The relation of creatin to creatinin is shown below:



Creatin. Creatinin.

What becomes of the "carbon moiety" of the proteid molecule, that large fragment which is not drawn upon in the formation of urea? Can it be stored in the body when not called upon for oxidation? Most physiologists have assumed that it may serve to build up fat or even glycogen under proper conditions. The criticisms of Pflüger and his school have thrown doubt upon many of the supposed instances of fat or glycogen formation from proteid. The "fatty degeneration" of organs has long been a favorite illustration of a similar reaction; but the tendency of modern research is to refer this phenomenon to a process of infiltration of fat imported from other parts of the body. In other cases the proteid is assumed to conserve the fat or glycogen of the body by its own oxidation and thus simulate fat or glycogen formation. The formation of tissue fat from the fats and carbohydrates of the diet is unquestioned; and while the data at hand regarding the direct formation from proteid may be unsatisfactory, the possibility of such a reaction can scarcely be denied. Carbohydrates are readily stored up as glycogen in the liver and muscles, and may also be found in other active tissues. The extent to which glycogenesis may go on is after all rather limited; and the unused carbohydrate may be deposited as fat for which there is an almost unlimited depot. How extensive distinctly synthetic processes may become, on the other hand, is illustrated in the transformations which result in the formation of milk within the mammary glands. The proteid, carbohydrates, and fat content of this secretion are almost entirely made up of compounds not found elsewhere in the organism.

The chemical changes within the individual organs and tissues have been referred to incidentally in various connections. The muscles are doubtless the most important in point of metabolic activity, owing to the large amount of contractile tissue in the whole body and to the vigorous oxidation going on in this. Among the glandular organs the liver stands pre-eminent as the seat of a series of important physiological functions, chemical in nature. In addition to glycogenesis and the reverse process by which sugar is again set free, the formation of urea from ammonia and amido compounds, and the oxidation or synthesis of uric acid, the liver is responsible for the formation of bile pigment from the blood constituents; for the preparation of cholic acid from antecedents not yet known and the origin of the conjugate bile acids; for the synthesis of the ethereal sulphates of the urine; for processes by which many toxic substances are rendered inert; and finally for a series of chemical processes of which we know only the merest outlines. The metabolic changes in the other gland cells are doubtless of a simi-

lar nature, although they may be less extensive or variable. In the salivary glands, for example, constructive metabolism goes on coincidently with secretory activity, and the glands tend, so to speak, to remain in nitrogenous equilibrium.

The importance of certain organs for metabolism is made evident by the effects of their removal from the body. After splenectomy or after extirpation of the salivary glands no marked general effects are apparent; and to a lesser degree this is true with reference to the ovaries and testes. On the other hand, the loss of the thyroids, the adrenal glands, the pituitary body, and the pancreas is in each case immediately followed by serious and usually fatal disturbances in metabolism. The functions of the "internal secretions" of such organs are slowly being exposed, and we may hope that the near future will greatly enlarge our knowledge of metabolism within the individual organs and the cells themselves.

Lafayette B. Mendel.

References to the Literature.

The following brief list of references to the literature is not intended to be complete in any way, but rather to serve as a basis for any more extended study of metabolism. Many of the experimental data referred to in the article have been taken from the papers here referred to.

Atwater and associates: Bulletins of the Office of Experiment Stations, U. S. Department of Agriculture. (Nutrition investigation.)
Atwater and Langworthy: Digest of Metabolism Experiments. U. S. Department of Agriculture, 1898. (Very valuable compilation.)
Atwater and Benedict: Memoirs of the National Academy of Sciences, viii., 1902. (Alcohol and metabolism.)
Bidder und Schmidt: Die Verdauungssäfte und der Stoffwechsel, 1852.
Gulewitsch: Zeitschrift für physiologische Chemie, xxx., 1900. (Urea.)
Hammarsten: A Text-Book of Physiological Chemistry. Translated by Mandel, 1900. (Statistics of nutrition.)
Herter: Chemical Pathology, 1902. (Pathology of metabolism.)
Hofmeister: Die chemische Organisation der Zelle, Braunschweig, 1901.
Katzenstein: Pflüger's Archiv, xlix., 1891. (Oxygen consumption.)
Loewi: Centralblatt für Physiologie, xv. (Proteid synthesis.)
Luciani: Das Hungern, 1890. (Experiments on Succi.)
Mendel and Jackson: American Journal of Physiology, iv., 1900. (Spleen.)
Mendel and Brown: *Ibid.*, iii., 1899. (Allantoïn; nuclein metabolism.)
Munk und Ewald: Die Ernährung der gesunden und kranken Menschen, 1895, Theil I. (Useful work on Nutrition.)
Munk, Senator, Zuntz, etc.: Virchow's Archiv, Supplement Band, cxxxi., 1893. (Hunger Experiments on Cetti and Breithaupt.)
von Noorden: Beiträge zur Lehre vom Stoffwechsel, 1892; Pathologie des Stoffwechsels, 1893. (Metabolism in disease.)
Paton and others: Journal of Physiology, xxviii., 1902. (Spleen.)
Pflüger: Various papers published in his Archiv.
Reichert: American Journal of Physiology, iv., 1901. (Food and Heat.)
Richet: Dictionnaire de Physiologie: article on "Chaleur."
Rosenthal: Du Bois Reymond's Archiv für Physiologie, 1889. (Calorimeter.)
Rubner: Various papers in the Zeitschrift für Biologie.
Schaefer: Text-Book of Physiology, i., 1898. (Metabolism.)
Schreiber: Ueber die Harnsäure unter physiologischen und pathologischen Bedingungen, 1899. (Nuclein metabolism.)
Sherman and Hawk: American Journal of Physiology, iv., 1900. (Sulphur and phosphorus metabolism.)
Tigerstedt: Lehrbuch der Physiologie des Menschen, i., 1897. (Apparatus and statistics.)
Volt: Hermann's Handbuch der Physiologie, vi., 1881. (Classic experiments on metabolism.)

METABOLISM, DISTURBANCES OF.—Under this caption will be considered in a general manner the incomings and outgoings of the food and oxygen essential to the maintenance of both normal and abnormal metabolism, but chiefly the latter. The abnormal changes must not be of sufficient magnitude, however, to cause perceptible macroscopic lesions in the bioplasm constituting the protoplasm of the various organs and tissues of the body, for if they are, the domain of well-defined pathology is entered. These minor deviations in metabolism, which are in all instances the precursors of well-marked lesions, are best determined by a quantitative study of the intake and output from the system of the nitrogen and carbon supplied in the food ingested.

For practical clinical purposes, however, this study is confined largely to the estimation of the elimination of the nitrogen in the urea, and of the many excretory by-products of which nitrogen forms an atomic part. Up to the present time this has been necessary because simple and practical methods for estimating quantitatively the elimination of the carbon contained in the excreta have not as yet been devised. On the other hand, if the results of metabolism are to be determined absolutely and with scientific accuracy, perfect quantitative analyses must be made of all the food ingested and of all the nitrogen and carbon eliminated in the excreta. Failure to attain even approximate accuracy in these two directions is the essential reason for most of the errors that have crept into the clinical deductions in connection with this important subject. Much of this error, however, can be eliminated by a careful application of the very accurate estimates and tables, relative to the composition and digestibility of the foodstuffs, that have been worked out by König,[1] Rubner,[2] Atwater,[3] and others.

Beginning with the digestive organs of the alimentary canal, the chief disturbance in their metabolism is indicated by diminution or by arrest of their secretory activity. So far as we know, the chemical composition of the unorganized ferment bodies is not changed. Therefore the modifications in the metabolism of the cells of the salivary glands will be indicated by a diminution in the excretion of ptyalin, or its elimination may be completely arrested. Its absence or its decreased elimination indicates that the bioplasm constituting the epithelial cells of the glands fails to take up the proteid constituents from the blood and isomerically transmute them into ptyalin, to this extent interfering with perfect digestion and later with general metabolism.

In the stomach similar disturbances are met with, but they are more complicated in character, because the gastric mucous membrane has for its function the production, out of the proteids taken up from the blood, of hydrochloric acid, rennin, and pepsin. Hence, a disturbance in the metabolism of the epithelial cells peculiar to this organ will result in decreased production of hydrochloric acid, rennin, and pepsin. Only one of the three may be decreased or arrested, or all may be absent at the same time from the gastric secretion. In this manner there will be produced varying degrees of disturbance in the metabolic action of the epithelial cells lining the gastric tubules. This will cause varying degrees of disturbance in the gastric digestion and act as another source of general malnutrition and metabolic disturbance.

What has been said regarding the changes in the secretion of salivary organs and of the glands of the stomach applies with equal force to the secretion of the pancreatic gland. Here, however, owing to the more complex function of the gland so far as its secretion is concerned, disturbance in its metabolism is more varied in character and disastrous in its results. There may be a diminution or an arrest in the secretion of the amylopsin, trypsin, or steapsin. One or all may be involved, thus indicating varying degrees and kinds of metabolic disturbance in the bioplasm of the cells. The supposed milk-curdling ferment of the pancreatic secretion may be defective or absent, and this indicates still another type of disturbance.

The same may be said of the glands and follicles contained in the mucous membrane of the intestinal wall, all of which point to a disturbance in the metabolic function or bioplasm constituting the cells that enter into their formation.

While it is impossible from a practical standpoint to secure directly the secretion of the pancreatic gland and that of the intestinal glands for analysis in the human subject, indirectly we are readily made aware of a decrease or arrest in the output of the enzymes contained in these secretions by an imperfect digestion of the foodstuffs, or by a putrefactive instead of the normal fermentation of the starches, sugars, fats, and proteids contained in the food.

The decrease or arrest of the hepatic secretion must also be taken into account in the study of disturbed metabolism when analyzed from the digestive viewpoint. While the bile is not generally considered as important a digestive fluid as some of the other glandular secretions that are poured into the alimentary canal, it cannot be eliminated from this problem of disturbed metabolism.