Your nutrition committee has indeed assigned me a difficult topic to cover in thirty minutes. As you are probably aware, most authors of current textbooks of biochemistry devote half of their attention to the metabolism of fats, proteins and carbohydrates and their interrelationships. Probably few things are more boring to the average "outside" reader of such materials than to be "swamped" with page after page of complicated metabolic schemes. Unfortunately nature's processes are not simple although we, as scientists, attempt simplification. The current fad, of course, is to wallpaper your wall with large "metabolism charts" and "plaster" your desk top with the smaller variety, with the apparent hope that some environmental influence will ingrain these schemes in your memory. This, of course, does not work and you, like I, must refresh your memory when asked to discuss such topics before an audience.

All I can hope to do this morning is to present my concepts of some of the more important metabolic interrelationships between fats, proteins and carbohydrates. In doing so, I will attempt to not bore you with chemical formulas but to consider the overall nature of these metabolic ties. I will oversimplify and abbreviate the topic by considering as carbohydrate, glucose and glycogen; as fat, triglyceride; and as protein, certain typical amino acids.

Role in Nutrition

Proteins, fats and carbohydrates constitute the old "nutritional trinity" which despite the recent emphasis on trace nutrients, are still the most important components of the diet, for without substrate, there is little significance in catalysis. Fortunately the balance between these components of the diet is not often critical; that is, the body metabolism is geared to handle widely different types of diet. One must, of course, provide the required quantities of the indispensable amino acids, and essential fatty acids and sufficient additional nitrogen to provide for the dispensable amino acids, nucleic acids, etc. as will undoubtedly be discussed by Dr. Mastelic and Dr. White. Beyond this, all three components of the "nutritional trinity" can provide energy for vital body processes and biosynthesis. The typical diet contains primarily carbohydrate, ample or excess nitrogen but often insufficient amounts of certain essential amino acids, and extremely variable quantities of fat. A calorie of energy in fat is essentially equivalent in the body to a calorie in carbohydrate, although there may be differences in the metabolites which accumulate in the body as will be discussed later. A calorie from protein, when corrected for the fact that the amino acids are not completely oxidized in the body (i.e., urea is excreted), is also essentially equivalent. The "best-balanced" diet is one in which the various nutrients are supplied in proportions to provide the body with absorbed nutrients which just meet the metabolic needs of the body at that
time. If this "best-balance" is not achieved the body, of course, has the ability to "reshuffle" the absorbed nutrients in order to maintain homeostasis. The less "reshuffling", the more energetically efficient is the utilization of the diet. Another way of stating this is: when the heat increment of feeding (or specific dynamic effect) is minimal, the diet is balanced. This is contrary to the early view that only excess feeding of protein raised the heat increment of feeding; any dietary deficiency or dietary excess will apparently result in a greater loss of heat.

Another very simple, but often overlooked facet of the nutritional relationships of these three major classes of nutrients is the effect of high fat diets on protein requirement. Many people are aware of the fact that, because fat is a more concentrated source of carbon and hydrogen than is carbohydrate or protein, it has a higher caloric density (i.e., a gram of fat yields about 2.25 times as much energy to the body as a gram of carbohydrate or protein). Also it is commonly realized that animals tend to restrict their feed intake in proportion to the caloric content of the diet. Thus, whenever protein or amino acid requirements are expressed as \% of the diet (but not as gm/day), the requirement increases as the caloric density of the diet increases (i.e., as the fat content of the diet increases). Such effects are substantial and may account for near doubling of the protein requirement, when expressed as \% of the diet. There may be other more subtle and less well understood nutritional interrelationships between these three nutrients. For example, carbohydrates can supply the carbon chains for synthesis of many of the dispensable amino acids while fatty acids cannot. Also, for the ruminant animal in which one is feeding the bacteria and protozoa of the rumen as well as the host animal, important nutritional interrelationships between these nutrients occur which will not be discussed here.

Body "pools" and storage

The "pool" of a material refers to the total amount of that material in any arbitrarily defined compartment. Thus, the protein of the body can be called the body protein "pool", etc. Body pool sizes of carbohydrate, fat, and protein differ greatly between each other and between individuals. The carbohydrate (mainly glycogen) pool is invariably low, with glycogen accounting for up to about 5\% of the weight of the liver and about 0.5\% of the weight of muscles. The energy stored as carbohydrate is rather rapidly "depleted" (i.e., within a day) when it is called upon to supply the energy requirement of the body as during fasting. The adipose tissue often provides a rather large storage pool of energy as triglyceride, which may be called upon particularly when the carbohydrate reserve is low. The protein pool is invariably large and although the present concept is that there is no true "storage" form of protein, many individual protein pools of the body turn over rapidly (i.e., the liver protein pool turns over with a half-life of about a week) and can provide for the energy needs of the body.

Each of the pools is in a dynamic state in which it is constantly being synthesized and broken down as has been well verified with isotope experiments. Different proteins, however, have vastly different turnover rates. For example, the major connective tissue protein, collagen, turns over at a very slow rate. One wonders if the turnover rates for lipid in various tissue sites of the body do not also vary greatly.
Definition of Metabolism

The term metabolism refers to all reactions of importance in either the absorption and synthesis or breakdown and excretion of tissue components. It has been arbitrarily separated into anabolism, or synthesis, and catabolism, or breakdown. The viewpoint a few years ago was that anabolism is just catabolism in reverse, the intermediates and catalysts being the same. It is now known that there are many examples in which anabolism and catabolism follow entirely different pathways. The advantage of such an arrangement in terms of control mechanisms is easily realized. For all three body components under consideration the synthesis is known to take place by a route distinct from breakdown, although many of the intermediate reactions are reversible. For example, glycogen is formed by the uridine-diphosphate-glucose pathway; fatty acids, from acetyl-CoA via malonyl-CoA; and proteins, by an activation mechanism distinctly different from reverse proteolysis.

The metabolic reactions of various tissue components such as fats, proteins and carbohydrates are usually considered separately. This is just man's way of simplifying a complicated problem. Metabolism is in fact highly integrated with many common intermediates between fats, proteins and carbohydrates. The intriguing, but as yet largely unexplained, aspect is just how the body governs the direction which a particular metabolite will take. Current concepts relate such control mechanisms to hormones, mass action effects, feedback effects, repression, induction, etc. In truth, most aspects of metabolic control still remain to be completely explained.

Glycolysis and the Tricarboxylic Acid Cycle

Without doubt most of you are familiar with the two terms, glycolysis and the tricarboxylic acid (TCA) cycle. However, I find many students who are familiar with all the intermediates of these metabolic schemes and know the chemical structure of each metabolite, but they do not realize just what the reactions have accomplished for the body. Therefore, I wish to spend a little time on their overall accomplishments in metabolism.

A simplified scheme of glycolyses is shown in Figure 1. This overall reaction, which can occur in the absence of oxygen, is simply a splitting of glucose into two, three-carbon units (lactic acid) and the net synthesis of 2 molecules of ATP by substrate level phosphorylation. This provides usable energy to the body.

A simplified TCA cycle is shown in Figure 2. The cycle is closely coupled with hydrogen (or electron) transport and oxidative phosphorylation outlined in Figure 3. In starting with two molecules of lactic acid, the overall reaction of the TCA cycle involves 6 molecules of H₂O as reactants to produce 12 pairs of H (or 24 H) and 6 CO₂. By electron transport and oxidative phosphorylation, which continue to operate only in the presence of oxygen, the 24 H become 12 H₂O (giving a net production of 6 H₂O) and the equivalent of 36 ATP's are produced from ADP. Actually one of the reactions (at succinic acid) of the TCA cycle taps in at FAD in the H transport scheme and bypasses one phosphorylation, but a closely allied reaction has produced the equivalent high-energy compound, GTP.
Figure 1 - Glycolysis (anaerobic metabolism)

Overall accomplishment from glucose:

\[
1 \text{ glucose} + 2\text{ATP} + 4\text{ADP} + 2\text{P}_i \rightarrow 2 \text{ lactic acid} + 4\text{ATP} + 2\text{ADP}
\]

\[
(C_6H_{12}O_6) + 2P_i \rightarrow (C_3H_6O_3)
\]

Net = 2ATP/glucose
Figure 2 - The Tricarboxylic Acid Cycle (oxidative metabolism)

Overall accomplishment:

\[
\begin{align*}
1 \text{ lactic acid} + 3H_2O + 1\text{GDP} &\rightarrow 12H + 3\text{CO}_2 + 1\text{GTP} \\
(C_3H_8O_3) \\
\text{or per glucose unit (C}_6H_{12}O_6) \\
2 \text{ lactic acid} + 6H_2O + 2\text{GDP} &\rightarrow 24H + 6\text{CO}_2 + 2\text{GTP} \\
(C_6H_{12}O_6)
\end{align*}
\]
Overall accomplishment from oxidation of lactic acid:

1 lactic acid + 3H₂O → 12 H + 3CO₂
(C₃H₆O₃)

+3O₂ + ~ 18 ADP

→ 6H₂O + ~ 18 ATP

or per glucose unit (C₆H₁₂O₆)

2 lactic acid + 6H₂O → 24H + 6CO₂

+6O₂ + ~ 36ADP

→ 12H₂O + ~ 36ATP
Figure 4 summarizes the overall oxidation of glucose and shows that the net reaction is simply the "combustion" of glucose to CO₂ and H₂O with liberation of part of the energy as heat; part of the energy is trapped as usable energy (ATP) for muscle contraction, biosynthesis, etc. The efficiency of trapping of the energy can be calculated to be about 40%.

**Fatty Acid Oxidation**

The scheme for fatty acid oxidation to acetyl-CoA is presented in Figure 5. The hydrogen atoms produced yield ATP by oxidative phosphorylation. The spiral signifies a repeat of the reactions until the entire fatty acid molecule is broken down to two-carbon units (acetyl-CoA). This acetyl-CoA can then enter the TCA cycle as in the case of glucose metabolism. Calculation shows that a net of 130 energy-rich bonds of ATP are formed from oxidation of the fatty acid, palmitic acid.

**Utilization of Protein for Energy and Conversion to Fat and Carbohydrate**

When the carbohydrate reserve of the body is depleted and particularly if the fat stores are also depleted, there is net catabolism of protein for energy. If excess protein is fed, the carbon chains may be used for energy or converted to carbohydrate or fat. Each of the twenty amino acids of proteins are metabolized by individual pathways and yield important individual metabolites, however, there are some general reactions of significance which apply to many or several amino acids.

**Figure 4 - Overall Oxidation of Glucose**

1. Glycolysis

\[ C_6H_12O_6 \rightarrow 2 C_3H_6O_3 \quad \text{(lactic acid)} - \text{net } 2 \text{ ATP} \]

2. TCA cycle

\[ 2 C_3H_6O_3 + 6H_2O \rightarrow 24 H + 6 CO_2 \]

3. Hydrogen transport and oxidative phosphorylation

\[ 24 H + 6O_2 \rightarrow 12 H_2O \]

**Sum:**

\[ C_6H_12O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O -- \text{ net } 38 \text{ ATP} \]
Figure 5 - Fatty Acid Oxidation
The α-amino groups are removed from the carbon chains of amino acids by deamination and transamination. A typical oxidative deamination is illustrated in Figure 6 for glutamic acid. All of the amino acids can undergo oxidative deamination to yield the corresponding keto acids, however many of the amino acid oxidases depend on FAD rather than NAD⁺. Transamination is also a reaction in which almost every amino acid participates and involves transfer of the α-amino group to a keto acid. Particularly widespread are transamination reactions involving glutamic acid. Such a reaction is illustrated in Figure 7. Both of the above reactions are readily reversible and account for the incorporation of amino groups from ammonia into amino acids as well as the removal of the ammonia from amino acids for final conversion to urea via the urea cycle. For some reason two amino acids, lysine and threonine, can be deaminated but are not synthesized from their corresponding keto acids. For the dispensable amino acids, the carbon chains can be synthesized in the body, while for the indispensable amino acids this does not occur to a sufficient extent to supply the body with that amino acid. It is easily seen that the carbon chains for some of the amino acids are intermediates of glycolysis and the TCA cycle (for example; pyruvic acid for alanine and serine, oxalacetic acid for aspartic acid and α-ketoglutaric acid for glutamic acid).

Amino acids are classified as either glucogenic or ketogenic depending on whether the carbon chains arising in their degradation are most readily converted to carbohydrate or to fat and ketone bodies. Before discussing this in detail it is necessary to integrate to some extent the metabolism of carbohydrate, fats and protein.

**Figure 6 - Oxidative Deamination of Glutamic Acid**

\[
\begin{align*}
&\text{COOH} \\
&\text{H}_2\text{N-CH} \\
&\text{CH}_2 + \text{NAD}^+ + \text{H}_2\text{O} \quad \text{glutamic dehydrogenase} \quad \text{COOH} \\
&\text{CH}_2 \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{C=O} + \text{NADH} + \text{H}^+ + \text{NH}_3 \\
&\text{COOH}
\end{align*}
\]

L-glutamic acid

α-ketoglutaric acid
Figure 7 - Transamination

\[
\begin{align*}
\text{H}_2\text{N}-\text{CH} & \quad \text{H}_2\text{N}-\text{C-H} \\
\text{CH}_2 & \quad \text{CH}_3 \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{COO}^- & \quad \text{COO}^- \\
\text{L-glutamate} & \quad \alpha\text{-ketoglutarate}
\end{align*}
\]

Some Metabolic Interrelationships Between Carbohydrate, Fat and Protein

Figure 8 depicts some of the interrelationships between carbohydrate, fat, and amino acids. This scheme is not intended to be complete nor are many of the intermediates indicated. Several points require comment. Two important, centrally-located reactions are for all practical purposes irreversible. These are the conversion of pyruvate to acetyl-CoA and of $\alpha$-ketoglutarate to succinyl-CoA. The significance of this irreversibility is that acetyl-CoA cannot act as a precursor for glucose or glycogen, while many of the TCA cycle intermediates are effective precursors of glucose. If the acetyl group is metabolized by the TCA cycle, two carbon atoms are lost as CO$_2$ before a carbohydrate precursor is formed, thus there can be no net synthesis of carbohydrate from fatty acids in animals. The glycerol moiety of fats may, however, be converted to glucose. Because some organs such as the brain require blood glucose for energy, it is of utmost importance that a certain circulatory level of glucose be maintained even when carbohydrate is not being absorbed and the supply of glycogen is nearly depleted. The glucogenic amino acids are of utmost importance in this regard. The majority of the amino acids are glucogenic as illustrated in Figure 8 (glutamic acid, aspartic acid, glycine, alanine, serine, valine and a number of others).

Also apparent from Figure 8 is the fact that carbohydrates and the carbon chains from amino acids are effective precursors of body fat.
Figure 8 - Examples of Interrelationships of Carbohydrate, Fat and Protein Metabolism
The central role of acetyl-CoA in the oxidation of fats and carbohydrates has been mentioned. In addition to entering the TCA cycle, acetyl-CoA serves as a precursor of several other products, including ketone bodies and cholesterol. When large amounts of fat are being metabolized with very little carbohydrate being metabolized, such as in starvation and particularly in diabetes, complications of ketosis arise. Acetyl-CoA is apparently formed at a more rapid rate than it can be handled by the TCA cycle and ketone bodies accumulate. While many organs and tissues (i.e., muscle) of the body can metabolize the ketone bodies for energy, the liver cannot do so. The excess ketone bodies are excreted and because two of these are acidic they pull sodium ions from the body. This lowers the base reserve and can result in acidosis. A number of explanations for failure of the TCA cycle to handle the acetyl-CoA of fat metabolism have been put forward, such as a relative lack of TCA cycle intermediates (i.e., oxalacetate) and excessive fat breakdown by the liver, but none has been universally accepted. One current idea is that triglyceride in the adipose tissue is being continuously broken down to fatty acids and glycerol and also is being synthesized. Resynthesis of triglyceride from glycerol apparently cannot take place in adipose tissue because of lack of the enzyme, glycerol kinase, which produces the necessary intermediate, α-glycerol-phosphate. The α-glycerol-phosphate comes instead from breakdown of glucose via dihydroxy-acetone-phosphate. Thus, the anabolic portion of fat metabolism depends on glucose metabolism by the adipose tissue. Presumably, if glucose is in short supply, the catabolism "overshoots" and too much fat is mobilized resulting in ketosis.

Some of the amino acids are also ketogenic and if supplied singly in fairly large amounts they will cause a ketosis. Particularly leucine and to some extent phenylalanine, tyrosine and isoleucine are ketogenic as is apparent in Figure 8. Some amino acids contribute some of their carbons to both glucose and ketone bodies and therefore are not really either glucogenic or ketogenic.

Fat mobilization from adipose tissues is a subject which only recently has yielded to investigation. Mobilized fatty acids circulate in the blood as albumin complexes, usually occur in inverse proportion to the level of blood glucose, and serve as effective sources of energy for many tissues of the body. Their turnover rate is exceedingly rapid and although they make up only a small portion of the total lipids of blood they are quantitatively very important energy sources. Their release from adipose tissue is, at least in part, under hormonal control.

Another interrelationship of current interest between carbohydrate metabolism and biosynthesis of fat (or any other reductive synthesis) is the so-called hexose-monophosphate shunt. Although this metabolic scheme will not be discussed in detail, it explains the conversion of glucose to pentoses and a number of other sugars and is an alternate route of glucose metabolism. Of significance is the fact that an early reaction of the shunt generates NADPH (or TPNH) rather than NADH (or DPNH) as in glycolysis and the TCA cycle. NADPH is the reduced coenzyme involved in many reductive syntheses such as the synthesis of fatty acids. It is believed therefore that when a major share of the glucose in a tissue is metabolized by the shunt mechanism, as opposed to glycolysis, fatty acid synthesis and other biosyntheses are favored. Perhaps this is one mechanism whereby the body controls the extent of synthesis versus the extent of complete oxidation.
This discussion has only touched on some of the more widely recognized interrelations of carbohydrate, fat and protein metabolism. I hope that I have not simply "rehashed" something you already know.

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MR. DOTY: I think it is obvious from this presentation why the committee felt that Dr. Hoekstra was uniquely qualified to present this rather involved and difficult subject; he made it seem so simple.

I would suggest that you withhold your questions until the end of the session, and refer them then to the proper person.

The second speaker of our group this morning is, again, I feel, extremely well qualified to talk about his subject. I have heard him discuss it; I am sure that some of you know him and recognize how close he has been to this whole subject of fats in human nutrition. Dr. Philip L. White, who is Director of the Department of Foods and Nutrition and Secretary of the Council on Foods and Nutrition for the American Medical Association, will talk about Fats in Human Nutrition.

DR. PHILIP L. WHITE: Thank you, Del.

Dr. Doty made the forthcoming presentation appear to be very simple, but to talk with you good people about animal fats in human nutrition does not appear to me to be simple, and the real reason being that I am quite certain that you know a great deal more about the subject than I do.